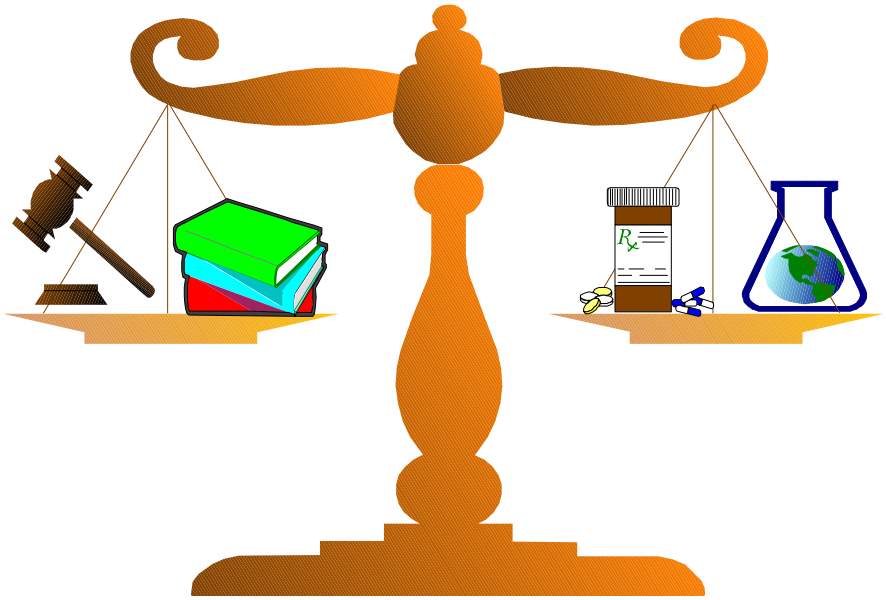
CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Compliance



Annual Report
Fiscal Year 1996

U.S. Department of Health and Human Services
Public Health Service
Food and Drug Administration.

DEDICATION

The Office of Compliance proudly dedicates their FY 1996 Annual Report to Frances O. Kelsey, MD, PhD, Deputy for Scientific and Medical Affairs, Office of Compliance, CDER.

While studying for her doctorate at the University of Chicago in 1937, she assisted in critical laboratory experiments on elixir of sulfanilamide which lead to identification of the poisonous ingredient, the solvent diethylene glycol. The deadly product was being used to treat children's infections. Deaths resulting from this drug led directly to the 1938 Federal Food, Drug, and Cosmetic Act. She received her medical degree in 1950 from the University of Chicago medical school.

Dr. Kelsey began her career with FDA's Bureau of Medicine as a medical reviewer on August 1, 1960. President John F. Kennedy awarded her the Distinguished Federal Civilian Service Medal of Honor in 1962 for her review of the drug thalidomide. Results of her review blocked marketing of the drug in the United States, thus preventing babies being born with severe neurological and birth defects as occurred overseas. The drug was being administered to pregnant women for morning sickness and insomnia. That event led to the 1962 Kefauver-Harris Drug Amendments which increased the agency's oversight authority.

In 1982, she joined the Office of Compliance as Director of the Division of Scientific Investigations. In this capacity she managed the Center's Bioresearch Monitoring Program for Human Drugs including: clinical investigations, bioequivalence studies, nonclinical laboratory studies, Institutional Review Boards, Radioactive Drug Research Committees, and sponsors and monitors of clinical investigations. In 1995, she assumed her current position as Deputy for Scientific and Medical Affairs, Office of Compliance.

In 1994, an elementary school in her hometown of Cobble Hill, British Columbia, was named in her honor. In addition, an asteroid, Minor Planet Kelsey, also carries her name. Dr. Kelsey has been invited by the Library of Congress to submit her personal papers to its archives. Her scientific documents will be preserved alongside those of other renowned scientists, such as anthropologist Margaret Mead and Harvey Wiley, considered the father of FDA.

PREFACE

The Office of Compliance is composed of the Immediate Office of the Director and four Divisions:

- The Division of Labeling and Nonprescription Drug Compliance
- The Division of Manufacturing and Product Quality
- The Division of Prescription Drug Compliance and Surveillance
- The Division of Scientific Investigations

The Office of Compliance is responsible for the effective and efficient management of high profile programs including the Center's Bioresearch Monitoring Program, Drug Quality Assurance Program, and (A)NDA Pre-Approval Inspections/Investigations Program for domestic and foreign-source drug products.

To increase the availability of safe and effective human drugs worldwide, the Office directs activities to harmonize international regulatory requirements and standards. We furnish technical expertise in support of the agency's initiative to establish Mutual Recognition Agreements and Memorandum of Understanding Agreements with foreign governments. We participate in international forums and meetings, such as the International Conference on Harmonization and International Standards Organization.

The Office assisted in developing a precedent-setting regulation on electronic records and electronic signatures. This regulation, linked to the reinventing government initiative, reduces the paperwork burden of the pharmaceutical industry, simplifies regulations, and speeds the filing process for drug applications and other regulatory documents. Proposed amendments to the good manufacturing practice regulation were formulated to clarify the requirements and reflect current agency interpretations and industry practice.

The Export Certificate Program was restructured to meet the statutory mandate of the FDA Export Reform and Enhancement Act of 1996. This Act requires that certificates for approved and unapproved drug products are issued within twenty days of receipt of a request.

In preparation for the future, the Office is focusing on technological advances and increased customer expectations. We developed and started new strategic initiatives and programs to meet government mandates and declining resources. Initiatives include the Establishment Evaluation System used to process Establishment Evaluation Requests. The system enhances communication and planning between the Office of Compliance, review divisions and the field offices.

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Message from the Director...

Dear Colleagues Everywhere:

We dedicate our Annual Report and the accomplishments it represents to Dr. Frances O. Kelsey, who is a continuing inspiration to us.

This year our Investment in Excellence program has paid handsome dividends. As you read this Annual Report for Fiscal Year 1996, I believe you will be impressed, as I have been, by the depth and breadth of accomplishments tallied by the four divisions and front office which make up the Office of Compliance.

I am proud of each individual and their joint contributions represented by this report. The way they achieved these accomplishments--through teamwork, integrity, tenacity, and devotion to the mission and ideals of the FDA in its 91st year--is as rewarding as the cumulative and impressive productivity. Among us we have earned 65 awards, including the 1996 Ronald H. Brown Award, the FDA Award of Merit, the FDA Commissioner's Special Citation, the Hammer Award and the Public Health Service Unit Commendation Award. The most effective group of men and women in the world are working together, and with you, to assure that quality drugs are available to all.

Stephanie R. Gray

Stephanie S. Gray
Director

Betty L. Jones
Deputy Director

Frances O. Kelsey, MD, PhD
Deputy for Scientific and Medical Affairs

I feel deeply honored that the Office of Compliance's 1996 Annual Report has been dedicated to me. It gives me the opportunity to review some of the scientific and regulatory changes I have seen over the past 60 years that helped assure the availability of safe and effective drugs for the American public. Things were very different when the Elixir of Sulfanilamide tragedy occurred in 1937. Under the 1906 Food and Drug Act a new drug could be marketed if the manufacturer considered it safe when used as directed. The onus fell on the Food and Drug Administration to prove otherwise. Dr. Geiling, Professor of Pharmacology at the University of Chicago and my PhD advisor, foresaw that the tragedy could lead to a much needed and long sought strengthening of the law. This is why he required all graduate students to assist with animal toxicity tests he had been asked to perform to determine the toxic component.

The 1938 Federal Food, Drug, and Cosmetic Act (the Act) afforded greater protection to consumers by requiring that proof of safety be presented to the agency before a drug could be marketed. While this requirement prevented the marketing of thalidomide in this country, weaknesses in the Act became apparent following the development of new and more potent drugs during and after World War II. When I joined the agency in 1960 as a reviewing medical officer in the former Bureau of Medicine, the drug approval process was under considerable criticism, particularly the quality of the scientific data submitted in the new drug applications and the lack of an efficacy requirement.

The nature and magnitude of the thalidomide disaster assured the October 1962 passage of the much debated Kefauver-Harris Amendments to the 1938 law along with last minute additional requirements for proof of efficacy and for obtaining consent from subjects receiving an unapproved drug. Realizing the need for closer oversight of investigational drugs, the FDA already published draft regulations for comment in August 1962. They were published in final form in March 1963 virtually unchanged except for the addition of the efficacy and the consent requirements of the 1962 law.

The 1962 amendments and 1963 regulations gave the FDA greater control and responsibility over the conduct of clinical and preclinical studies. Well before thisreviewers in the Bureau had grave doubts about the integrity of certain clinical

investigators. In 1961, a reviewer, Dr. John Nestor, was authorized to visit one such investigator. Dr. Nestor uncovered serious irregularities, and in 1963, the clinical investigator became the first to be declared ineligible to receive investigational drugs under newly drafted procedures. Between 1963 and 1966 the Investigational New Drug Applications (INDs), then known as Notices of Claimed Exemption for a New Drug, were reviewed by a separate IND Branch that also undertook further inspections of suspect investigators. The work was facilitated by abstracting data from INDs and New Drug Applications (NDAs) in readily retrievable form at first using IBM punch cards (Project RAPID) and then by computer techniques.

The IND Branch was abolished in 1966 and the review of INDs and NDAs was divided among six review divisions. In 1967, a separate group, the Scientific Investigations Staff (renamed the Division of Scientific Investigations in 1971), was formed to continue oversight of clinical investigators suspected of submitting unreliable results. In 1971, a pharmacologist was added to the staff to inspect laboratories submitting suspect preclinical (animal) studies. The serious problems that were uncovered stimulated the development of the Good Laboratory Practice (GLP) Regulations. Initially attention was focused on inspections of clinical investigators known or suspected to have submitted false data or who had conducted studies on vulnerable subjects such as prisoners, children, the mentally incompetent, and the elderly. By 1976, the approach was broadened to include verification of all studies considered pivotal to approval of a new drug with a view to avoiding approval on the basis of faulty data.

It soon became apparent that many physicians were failing to obtain patient consent. A policy statement issued in 1971 indicating the information subjects should be given and under what circumstances the consent must be in writing--details which had been lacking in the 1962 law and 1963 regulations. Some seriously deficient studies conducted on prison subjects prompted a 1972 requirement for the review and approval of studies involving institutionalized subjects by an independent committee. The Division of Scientific Investigations started limited surveillance of these committees in 1972. Surveillance was greatly increased after 1981 when the requirement for review and approval by an independent committee was extended to all investigational drug studies.

The thalidomide disaster led to the strengthening of drug control laws in a number of other countries, many of whom lacked protection comparable to the FDA's 1938 law. The disaster also prompted exchange of information between governments. This is exemplified by the ongoing Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) between the European Union, Japan, and the United States. A number of guidance documents have been developed including one for Good Clinical Practices. It is expected that these documents will lead to a common dossier that will expedite the approval of safe and effective drugs and reduce human exposure to unapproved drugs.

OFFICE OF COMPLIANCE

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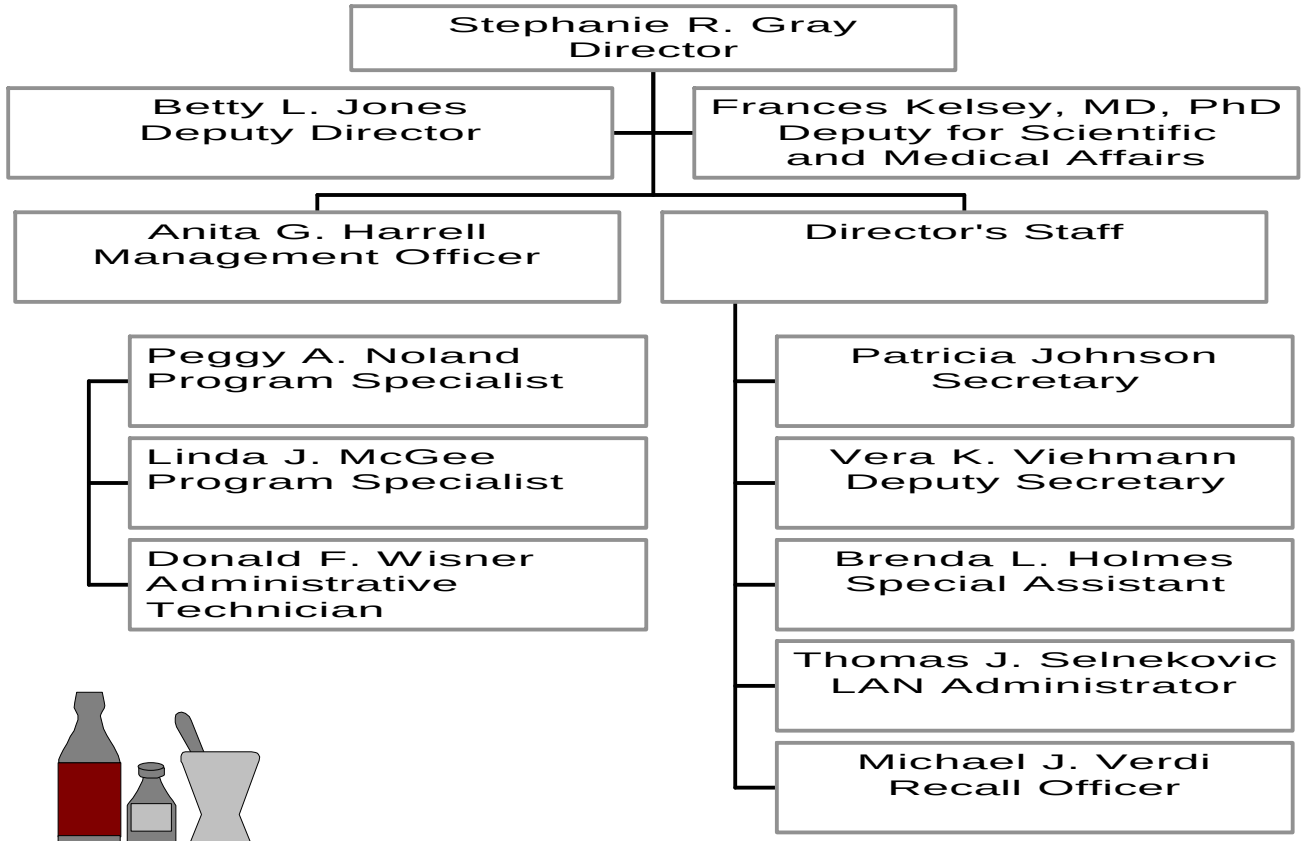
Clinical Investigations Branch	HFD-344			
	Bette Barton, MD, PhD	125	594-1032	MPN 1

OFFICE OF COMPLIANCE
Office of the Director



OFFICE OF COMPLIANCE

MISSION STATEMENT

The Office of Compliance assures that safe and effective drugs are available to the American people.

OPERATING PRINCIPLES

We are honest and fair.

We promote leadership by improving programs and applying rational strategies and creative solutions to problems.

We discuss information and ideas openly.

We make timely and comprehensive decisions based upon the best science and reasoning available.

We take responsibility for our actions and decisions.

We value our employees and encourage and support their ideas and contributions.

We interpret and enforce FDA laws and regulations uniformly and consistently.

We foster mutual trust with the public and the regulated industry.

HUMAN DRUG RECALLS

Introduction--It has been suggested that the concept of recall derives from biblical times when a trader accepted the return of a lame donkey. For our purposes, we can start with the twentieth century. This period simultaneously encompasses the development of modern American commerce, the population explosion, the emergence of consumer activism and the involvement of government in product regulation. In government and industry during the early days of this century, recall was an infrequent practice because (1) there were not as many people or products as today, (2) much of the industry was still in the cottage stage, and (3) production and distribution were primarily local. However, terms like corporate structure, mass production, and national distribution were just around the corner.

In 1916, the courts ruled that Buick Motor Company could not avoid responsibility for defective wheels bought from another manufacturer. This was a landmark case in product liability law that helped to establish a major incentive for recall by the manufacturer of hazardous or defective products. The role of Congress was strongly evidenced with the case of Sulfanilamide, a medical elixir, which in 1937 caused 107 deaths, led to the most dramatic recall of that time, and was the basis for the original Food, Drug and Cosmetic Act. The Food and Drug Administration (FDA) inspectors literally visited each consumer's home to track down the drug.

The next evolutionary turn in the history of modern recall began sometime after World War II when volume and diversity of consumable products began to assume today's proportions. By mid-century, both regulators and industry began to consider and to accept the advantages of recall over other alternatives for dealing with defective products. The FDA welcomed the procedure as an adjunct to the regulatory tools of injunction, seizure and prosecution. Recall was generally faster and more efficient and less demanding of public time and resources. Industry liked the procedure because recall could often be accomplished without publicity. Therefore, it offered an unobtrusive way of getting harmful or defective product lots out of commerce without damaging the reputation of an entire line of products.

This era of the "silent recall" ended abruptly in the mid-1960s when the consumers' movement entered the American scene. The recall process continued and expanded during this period due to two primary factors: (1) Congressional mandate of recall into the operational authorities of new agencies, and (2) an increase in the number of product recalls. Within FDA jurisdiction alone, the annual number of reported recalls has grown from several hundred in the early sixties to 1,500 in the mid-seventies to more than 3,400 in 1994. These figures include foods, drugs, cosmetics, devices and biologicals.

Today most of the industry accepts recalls as a needed process to be used openly and fairly with the consumers and government. The need for the recall process will endure as long as man and technology remain imperfect because recall, however useful or expedient, represents the result of failed quality control, a flawed process or production error after the fact. In all recalls everyone loses something because it demonstrates a problem that must be corrected. The consumer loses a wanted or needed product, the company loses profit and credibility, and the government loses time and money derived from public resources.

The current law provides for FDA-mandated recall for infant formula products and degrees of authority for medical devices, radiation emitting devices and biological products. This authority does not extend to other FDA regulated products. Revised or additional legislation would be required to expand that authority.

Human drug recalls have multiple origins. The most common origins are as follow: product testing by industry, NDA/ANDA-required reports and alerts, FDA inspection and sample surveillance, reports from health professionals, and consumer complaints. With rare exception, drug recalls are initiated by the firms after a determination that a violative product has been marketed. When a serious or significant health hazard has been identified and the responsible firm is reluctant to recall the product, a FDA-requested recall may be initiated by the Associate Commissioner for Regulatory Affairs.

Purpose--The objective of human drug recalls is to remove unsafe or violative products that pose a threat to public health or products that are deceptive or otherwise defective from the marketplace. Recalls may be voluntarily undertaken anytime by manufacturers and distributors or at the request of the FDA when the products may pose a threat. FDA-requested recalls are reserved for urgent situations or when firms fail to accept responsibility for the removal of violative products from the marketplace. It is directed to the firm that has primary responsibility for the manufacture and marketing of the product.

When many drug product lots have been widely distributed, a recall is generally more appropriate and affords better protection for consumers than seizure. It is an alternative to a FDA-initiated court action to remove violative products from the marketplace. Seizure or other court action is necessary when a firm refuses to undertake a recall requested by the agency, or if the agency thinks that a recall would not be effective, determines that a recall is ineffective, or discovers that a violation is continuing. Regulations detailing agency policy on product recalls are in the Code of Federal Regulations, Title 21, Part 7.

Program Description--Drug product defects are identified through a variety of sources, such as, establishment inspections, survey samples, or reports received through MedWatch or from manufacturers, wholesalers, retailers or consumers. Recalls
initiated by a firm without FDA involvement are considered firm-initiated. If the agency contacts a firm about a potential product problem and some recall action results, the recall is considered FDA-initiated. In addition, a recall may be formally requested by the agency.

If a firm decides to remove or correct a distributed product because it believes the product is violative, the firm is requested to notify the agency of the details of the recall. The details should include a product name, the reason for removal, production and distribution information, a risk evaluation, proposed recall communication and strategy, and an official firm contact person. The removal or correction will only be considered a recall if the product involves a violation subject to legal action.

The agency, as part of the recall process, conducts a health hazard evaluation considering such factors as: (1) has product use resulted in disease or injury, and (2) do conditions exist that could expose humans to a health hazard. Also considered are assessments of the hazard to population segments, the severity of the hazard to which populations at risk would be exposed, the likelihood the hazard will occur, and the immediate or long-range consequences should the hazard occur.

Based on the health hazard evaluation, the recall will be assigned a numerical classification of I, II, or III by the Center's Recall Coordinator. The designation assigned to a product suggests the relative degree of health hazard presented by the product being recalled.

- Class I is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.

- Class II is a situation in which the use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

- Class III is a situation in which the use of, or exposure to, a violative product is not likely to cause adverse health consequences.

For Class I recalls, the agency issues a letter identifying the recall classification and elements of a recall strategy to the firm. The recall strategy is developed by the agency for FDA-requested recalls and by the recalling firm for firm- and FDA-initiated recalls.

Recall strategies address the elements of depth, warning, and effectiveness. A public warning is reserved for urgent situations and, if needed, a recall strategy will specify whether the warning will issue through the general news media or specialized news media such as professional or trade press. The results of the health hazard evaluation, the ease in identifying the product, the degrees to which the product remains unused in the marketplace, and the continued availability of essential products are factors considered in the development of general recall strategies.

The recalling firm is responsible for promptly notifying each of its affected accounts. Recall communication may be accomplished by telegrams, mailgrams, or first-class letters conspicuously marked (preferably in bold red type on the letter and envelope), DRUG RECALL. In addition, for Class I and II recalls the letter and envelope should also be marked URGENT.

The recalling firm is requested to submit periodic recall status reports to the agency. The frequency of these reports is determined by the urgency of the recall and should include the following:

- The number of consignees notified of the recall and the date and method of notification,
- The number of consignees responding to the notice and the quantity of products on hand when the notice was received,
- The number of consignees that did not respond,
- The amount of a drug product returned or corrected and the quantity accounted for by each consignee contacted,
- The number and results of effectiveness checks made,
- The estimated time frames for completion of the recall.

The agency conducts audits to assure that the recall is effective and that the disposition of recalled products is being monitored or verified. The appropriate FDA District Office will perform an effectiveness check to verify that the firm's recall notification has reached those consignees specified in the recall strategy and that they have taken appropriate action. Consignees may be contacted by personal visits, telephone calls, letters, or a combination of methods. The recall strategy will specify the method(s) to be used and the effectiveness level. The five levels of effectiveness show the percentage of consignees (from zero to 100 percent) to be contacted. If the recall effort is ineffective, the agency will contact the recalling firm to determine how they intend to improve its effectiveness.

When the agency concludes that the recall was effective and that appropriate disposition of the recalled product is complete, the recall will be terminated. The agency gives written notification of termination to the recalling firm.

Program Accomplishments--During fiscal year 1996, 279 drug products were recalled from distribution channels. These represent 226 prescription drug products (47 of which were parenteral products) and 53 over-the-counter drug products. Three recalls were classified as Class I, 156 were Class II, and 120 were Class III. See charts pages 23-29.

Compliance Activities--Of the 279 recalls conducted during fiscal year 1996, one recall was requested by the agency, 96 recalls were FDA-initiated and 82 recalls were firm-initiated.

The ten top reasons for recalls during fiscal year 1996 were:

1. Deviations from Current Good Manufacturing Practice
2. Subpotency
3. Dissolution failure
4. Pyrogen test failure
5. Presence of foreign substance(s)
6. Label mix-ups
7. Stability data does not support an expiration date
8. Product lacks stability
9. Content Uniformity requirement failure
10. pH failure

HUMAN DRUG SHORTAGES

Introduction-- Drug shortages have resulted from production problems; quality, marketing and/or profitability concerns; unanticipated increases in demand; and distribution problems. Most shortages have been associated with single-source dosage forms and active ingredients. The agency recognizes that a shortage of a medically necessary drug product can have a significant impact on the public health. It is agency policy to attempt to prevent or alleviate such shortages.

Purpose--The Office of Compliance has an important role in the prevention and management of drug shortages. At times, administrative and regulatory actions have affected supplies of medically necessary products. This Office is responsible for reviewing and approving regulatory action recommendations to achieve compliance with the law. Simultaneously, when in the best interest of public health, the Office is charged with ensuring that the production and distribution of medically necessary products are not affected.

Program Description--In November 1995, the Office of Compliance issued a MaPP (Manual of Policies and Procedures) 4730.1, Drug Shortage Management, establishing Center-wide procedures for handling shortages of medically necessary drug products. A product is considered medically necessary, or a medical necessity, if it is used to treat or prevent a serious disease or medical condition, and there is no other available source of that product or an alternative drug judged by medical staff to be an adequate substitute. Patient "inconvenience" alone is an insufficient basis to classify a product as a medical necessity.

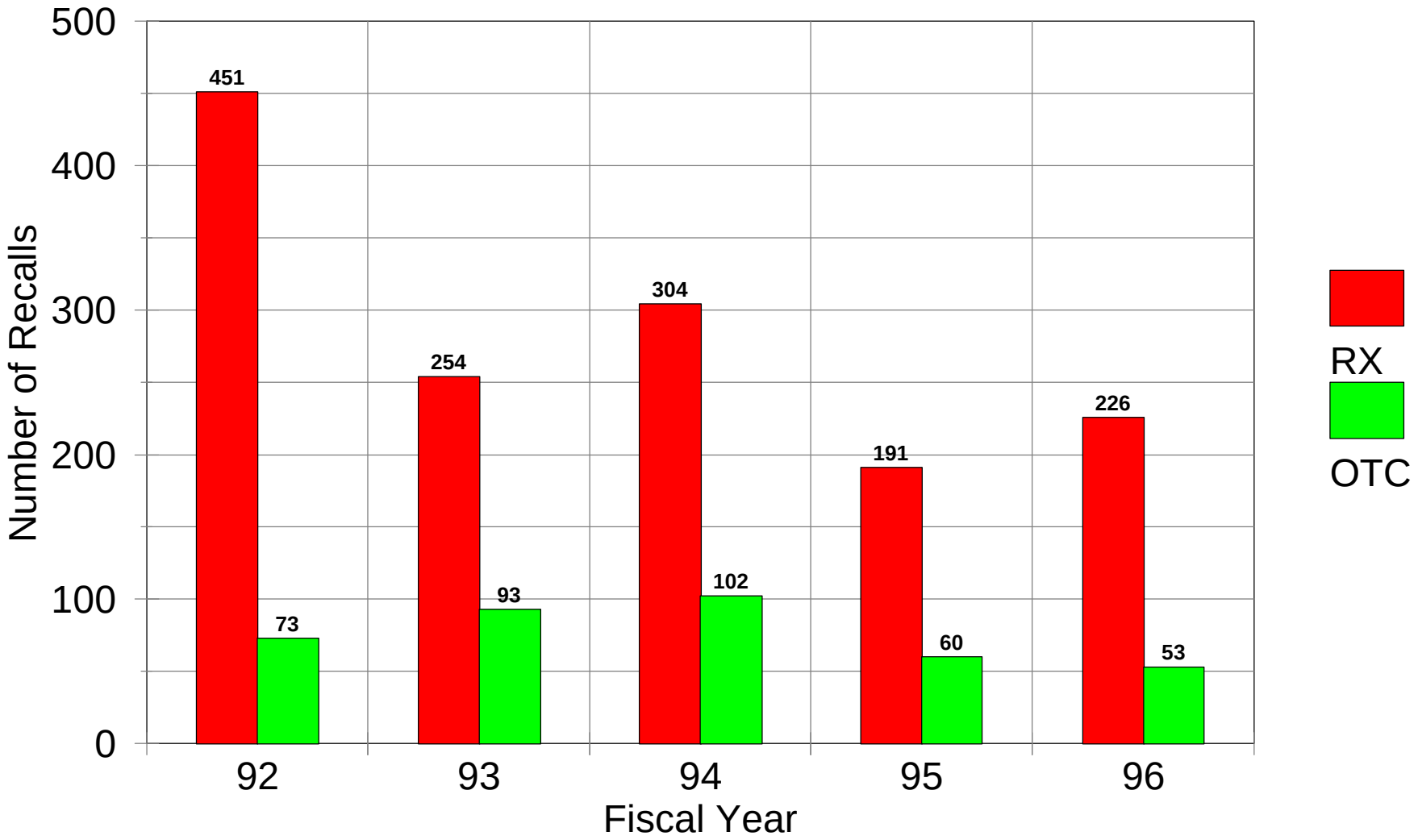
The MaPP distinguishes shortages of medically necessary drugs as enforcement-related and nonenforcement-related. Enforcement-related shortages are primarily managed by the Recall Coordinator in the Office of Compliance. Nonenforcement-related shortages (e.g., resulting from a business decision to cease marketing an unprofitable product) are primarily managed by the Office of Pharmacovigilance and Epidemiology and the appropriate review division.

The agency receives reports of drug shortages primarily from pharmacists reporting through the agency's MedWatch program. Other sources are FDA field offices, consumers, and the pharmaceutical industry. Shortage reports are forwarded to the offices identified in the MaPP for a medical necessity determination and confirmation that the product is or will be in short supply. Product shortages for medically necessary drugs are given priority review and compliance attention. Timely and effective

resolution of the shortage requires industry participation.

Program Accomplishments--During fiscal year 1996**,** the Office of Compliance received 46 reports of potential drug shortages. Fifteen reports were determined to be shortages of medically necessary drugs that required intervention by the Office of Compliance. The most labor-intensive shortage events involved products used as an antihypertensive agent, an antidote to treat acute iron intoxication, and a multivitamin for infusion.

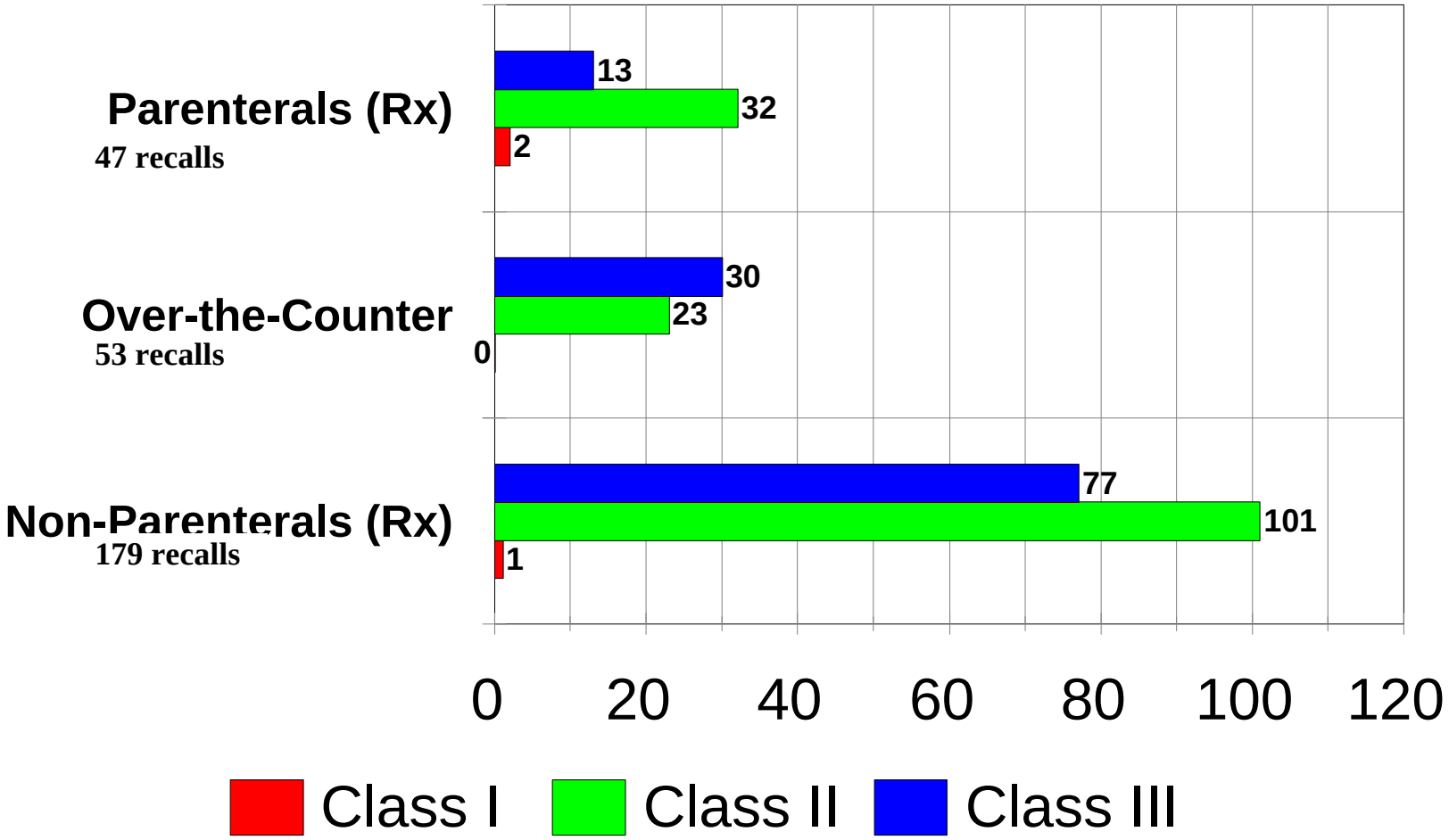
Human Drug Recalls



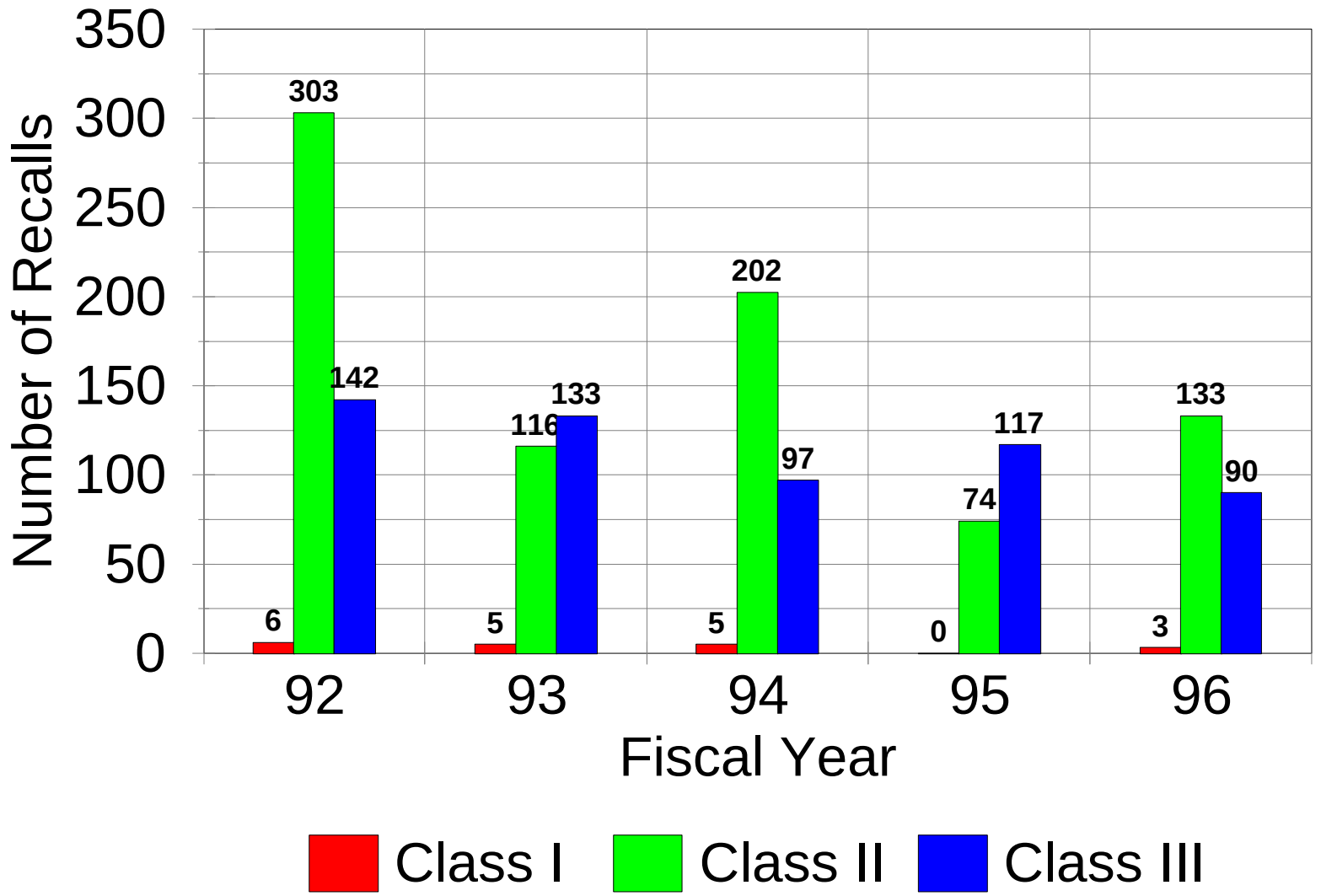
*** 143 recalls during Fiscal Year 1992 involved three drug firms that experienced GMP (Good Manufacturing Practice) problems, and/or ANDA discrepancies and lack of assurance of bioequivalency.**

Human Drug Recalls

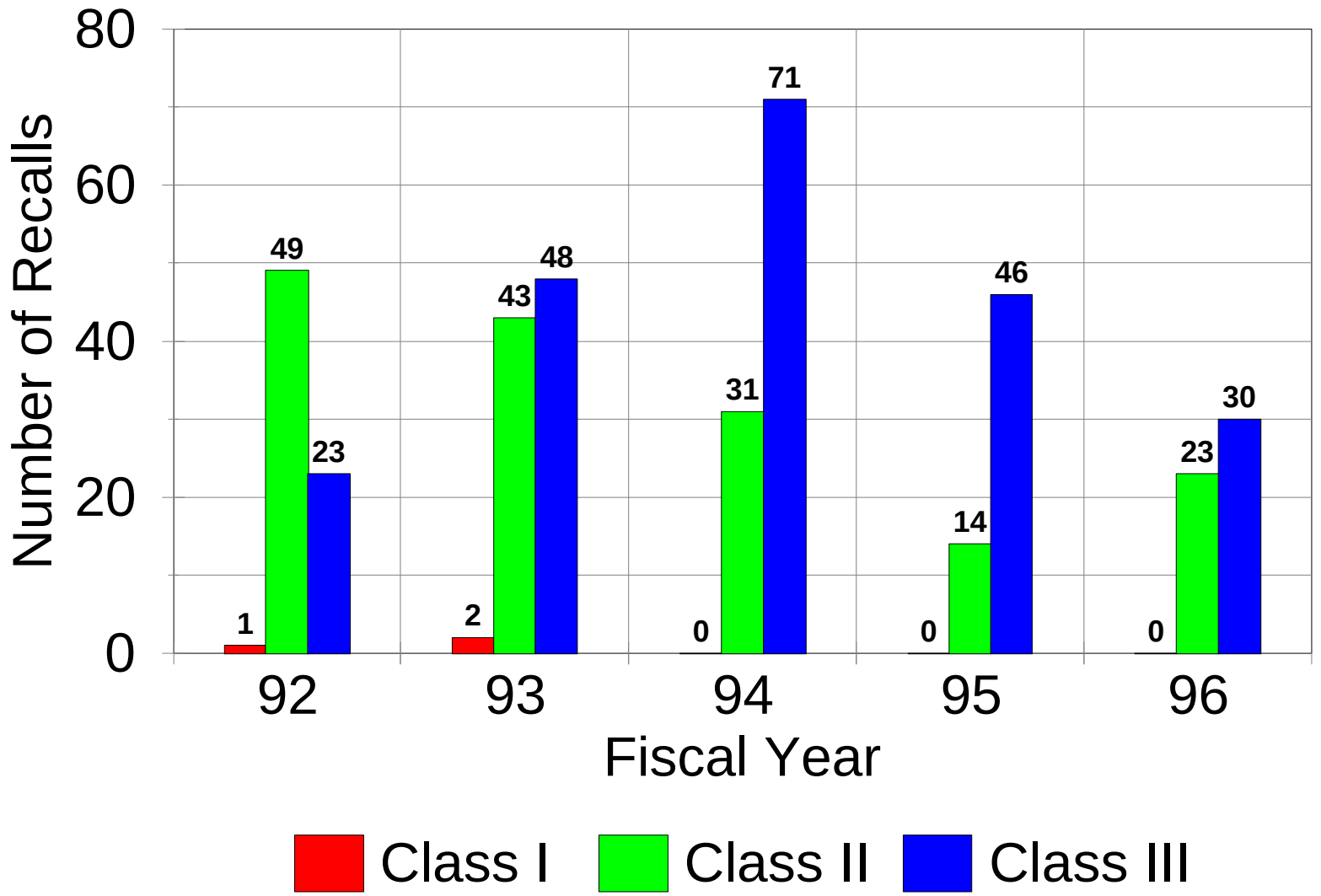
Fiscal Year 1996



Rx Drug Recalls



OTC Drug Recalls



LABELING AND NONPRESCRIPTION DRUG COMPLIANCE

Brad Williams
Director

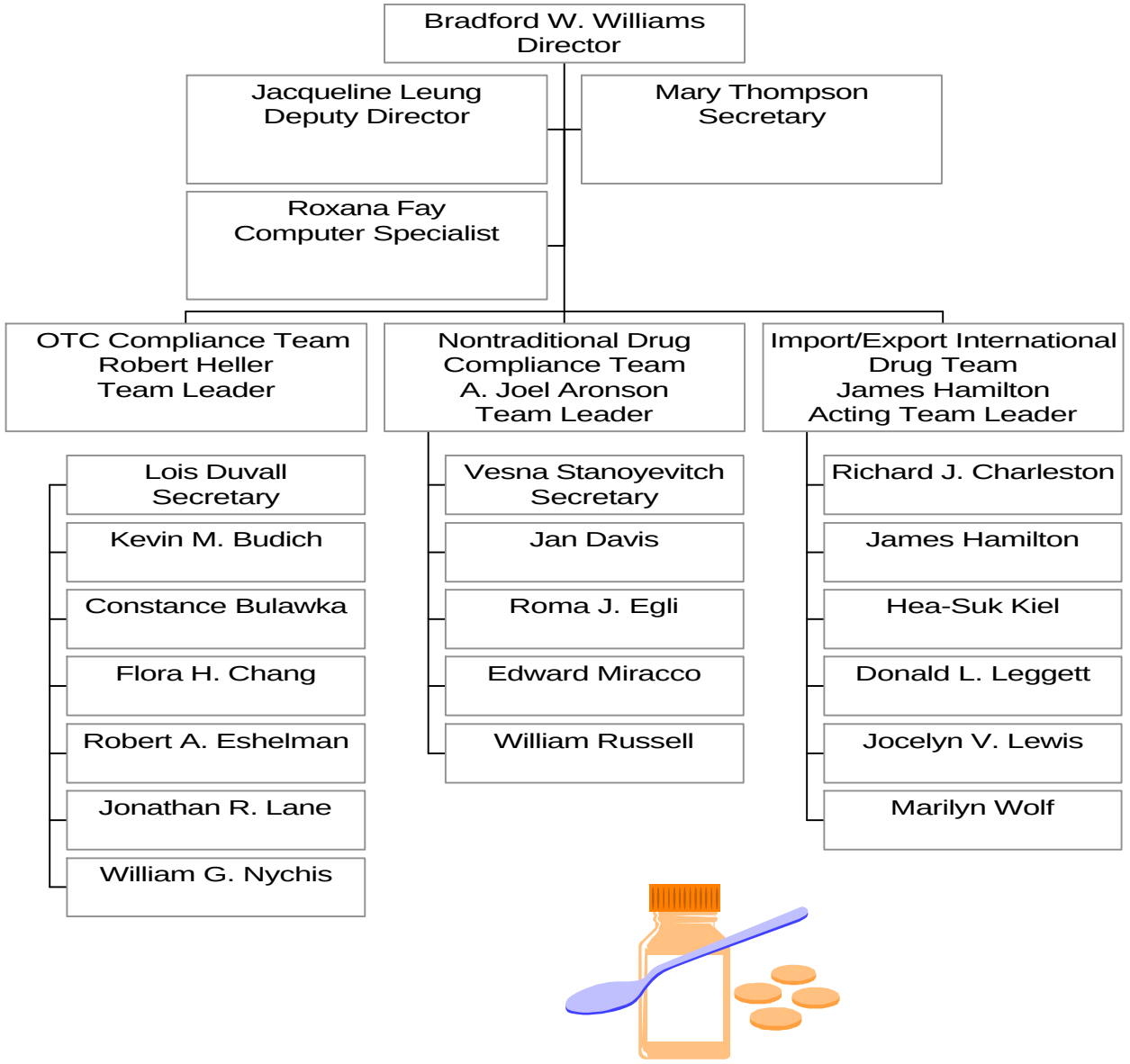
Jackie Leung
Deputy

The Division of Labeling and Nonprescription Drug Compliance is composed of the Over-the-Counter Compliance Team, the Nontraditional Drug Compliance Team, and the Import/Export International Drug Team. The division's primary responsibilities include enforcing the misbranding and new drug provisions of the Federal Food, Drug, and Cosmetic Act (the Act) for over-the-counter drug products. The principal program areas are as follow:

- Over-the-Counter Drug Monograph Compliance Program
- Nontraditional and Fraudulent Drugs Compliance Program
- Import/Export Program (Export Certificate Program)
- Drug Diversion and Counterfeit Drug Program
- Drug Listing Compliance Program

The division has reprioritized its responsibilities to enhance performance in giving policy guidance and managing complex regulatory issues.

Division of Labeling and Nonprescription Drug Compliance



DIVISION OF LABELING AND NONPRESCRIPTION DRUG COMPLIANCE

MISSION STATEMENT

We serve the American people by:

- Ensuring that all marketed over-the-counter (OTC) drugs and alternative medicines are safe and effective for their intended uses and are properly and legally labeled
- Providing guidance and interpretation of agency drug establishment registration and drug product listing regulations involving domestic and imported drug products
- Promoting goodwill and cooperation between the United States and foreign governments through the Export Certificate Program
- Assuring the integrity of imported and exported drugs by monitoring investigational and unapproved new drugs
- Identifying and addressing fraudulent or hazardous drug products that present a direct or indirect health hazard to the public
- Giving enforcement strategy guidance for scientific and legal support of criminal prosecutions involving diverted and counterfeit drugs

OVER-THE-COUNTER DRUG MONOGRAPH IMPLEMENTATION COMPLIANCE PROGRAM

Introduction--Over-the-counter (OTC) drugs are purchased in the United States without a prescription. These drugs have a significant role in maintaining and improving public health and minimizing public health care costs. In 1974, at the outset of the agency's OTC Drug Review, the division's OTC Compliance Branch was reorganized as the OTC Compliance Team. The team remains responsible for the uniform implementation of policy and enforcement of laws and regulations governing the labeling and formulation for OTC human drugs.

The division determines the drug and new drug status of proposed and marketed OTC products. The division assesses drug products' conformance with fifty-seven final monographs, twenty-seven pending monographs, and several other rules implemented under the agency's OTC Drug Review, including many requirements for drugs not subject to final monographs under the review.

Purpose--The OTC Drug Monograph Implementation Compliance Program assures the systematic enforcement of final OTC drug monographs and other regulations under the OTC Drug Review. Final OTC drug monographs establish conditions under which OTC drugs are generally recognized as safe and effective and not misbranded under the Act. This program identifies drugs legitimately deferred to the OTC Drug Review but not yet subject to final monographs/rules and the enforcement of existing regulations. This program identifies unapproved OTC new drugs in the marketplace and facilitates appropriate agency action. Program objectives are as follow:

- Determine if a product complies with the OTC review or is a new drug without an approved NDA/ANDA,
- Review and approve/disapprove regulatory actions for OTC drugs recommended by the field offices,
- Initiate regulatory action based on reviews of OTC drug product labeling, injury complaints, and consumer and industry complaints,
- Develop and issue investigational guidance, i.e., Program Circulars and OTC Drug Study Bulletins,
- Issue field assignments to obtain formulation, labeling and marketing information, and evaluate the information to determine the regulatory status of newly marketed OTC drugs not covered by NDAs.

Program Description--The program outlines agency enforcement strategy for final monographs and other rules established under the OTC Drug Review. This review consists of the following three-step process to establish which OTC drugs are generally recognized as safe and effective (not new drugs) and not misbranded:

- An advisory panel reviews data submitted for a class of drugs and publishes its findings in the *Federal Register* as an Advance Notice of Proposed Rulemaking.

- The panel's report and comments submitted from the public and industry are evaluated and the agency publishes a Proposed Rule in the *Federal Register.*

- Additional comments and data submitted in response to the Proposed Rule are reviewed and the agency publishes a Final Rule in the *Federal Register.*

Final monographs and other rules generally become effective one year after publication. Guidance for the OTC drug review process is in the Compliance Program.

The division develops and issues Program Circulars and Drug Study Bulletins. These bulletins alert the field to developments in the review process**,** and request that the field conduct follow-up as instructed in the program. Other Compliance Policy Guides affecting OTC drugs have been developed and issued by the division and are in effect until publication of final monographs for specific classes of products.

The division reviews all regulatory actions recommended by the field offices for OTC drugs, to assure uniform interpretation and application of the law and pertinent OTC drug labeling rules. This ensures that the regulated industry receives fair and equitable treatment. The division facilitates educational and compliance information activities with the nonprescription drug industry and trade associations, and conducts presentations, training, and individual meetings to discuss and suggest resolution of identified issues.

Program Accomplishments--During fiscal year 1996, five Drug Study Bulletins were issued and because of field assignments, the division initiated investigations of newly launched OTC drugs and/or emerging trends in the marketplace. Review and evaluation of thirty regulatory action recommendations resulted in issuance of twenty-eight warning letters and two seizures of violative products. The division assisted New Drug Evaluation Teams in evaluating labeling for ten drug products considered for switching from prescription to OTC status. The division contributed to

the processing and review of approximately 4,500 Certificates to Foreign Governments under the Export Certificate Program, and answered twenty-eight Freedom of Information requests and many inquiries for information. Division staff provided advice, consultation, recommendations, and guidance to the regulated industry, other agency units, State and local government officials, legislators, foreign government officials, and consumers.

Compliance Activities--Besides formal regulatory actions, the division responds to many inquiries on the acceptability of proposed products intended for marketing. This helps deter the marketing of possibly violative products. Because the OTC industry includes a large percentage of small operations, this advice prevents misbranded drugs and those of unknown safety and effectiveness from reaching the market.

The division provides specialized expertise when reviewing labeling requirements for prescription drugs being switched to over-the-counter status. Although prior agency review of labeling for non-NDA OTC products is not required, many firms request this review before marketing.

The division participated in the review of the agency's tobacco proposal, in the special review of OTC products with dual status (e.g., drug/device, drug/cosmetic, drug/food) and in cooperative efforts with the Center for Food Safety and Applied Nutrition for the regulation of vitamin, mineral, botanical and/or herbal preparations.

NONTRADITIONAL AND FRAUDULENT DRUGS COMPLIANCE PROGRAM

Introduction--The Health Fraud Staff was established in 1984 and was renamed the Nontraditional Drug Compliance Team. The team is the agency's focal point for fraudulent products and evaluates nontraditional and homeopathic products. The agency's regulation of nontraditional drugs resulted indirectly from a four-year Congressional review of the impact of quackery on the elderly. The report specifically identified ways that the agency can address health fraud issues in the United States.

Purpose--The purpose of the Nontraditional Drugs Compliance Program is to detect fraudulent drug products that pose a health hazard to the public through deceptive and misleading promotions. These products include those that are likely to:

- Directly cause death, injury, or other serious adverse effects when used as directed, and

- ♦ Indirectly cause harm to consumers who rely on an ineffective product with exaggerated or false claims resulting in the delay or discontinued use of appropriate medical treatment.

Program Description--Products are drugs when the labeling makes claims for preventing, treating, or curing disease. Nontraditional drug products that are likely to cause injury, death, or other serious adverse effects when used as directed are given priority. These products are direct health hazards and require immediate attention for removal from the market.

Most products encountered by the division are vitamin, mineral, amino acid, and herbal products with labeled drug claims. These products may be labeled as dietary supplements but make claims that they are safe and effective for the prevention, treatment, or cure of such diseases as AIDS, cancer, Alzheimer's, Parkinson's, diabetes, or multiple sclerosis. Because these claims may be unsubstantiated, there are potential implications that the products may pose an indirect health hazard to the consumer. When necessary, this division initiates negotiation or enforcement actions to remove these products from the marketplace.

The Act limits the inspection of an establishment for an OTC drug product to all pertinent equipment, finished and unfinished materials, containers, and labeling. The division uses various methods for obtaining information including ordering and purchasing products and reviewing various print media including the Internet.

The division monitors possible health fraud activities by issuing Health Fraud Bulletins. These bulletins alert the field offices to possible health fraud products, and give them guidance for handling the products and surrounding issues. Homeopathic drug products are a meaningful part of the program responsibilities. Although several bulletins refer to these products, homeopathics as a class are not regarded as fraudulent. They are organizationally assigned to this division, but their regulation is unique to the specific product. The agency's authority for potential health fraud products has been significantly modified because of the Dietary Supplement Health and Education Act of 1994 (DSHEA). Enacted in October 1994, DSHEA allows products defined as dietary supplements to bear structure/function claims without causing the products to be classified as drugs.

Program Accomplishments--During fiscal year 1996, several products considered significant health hazards were identified. These products were either removed from the market, are being removed from the market, or are undergoing further evaluation within the agency. The division approved fourteen warning letters, two seizure recommendations and one injunction, and gave guidance on two prosecution cases involving an unapproved antiwrinkle cream product and a purported homeopathic drug product. The division contributed to the agency obtaining a contempt of an injunction order against a firm for continuing to sell an AIDS Treating Machine with a drug solution.

Compliance Activities--The division assists other agency units and Federal agencies in developing policies and sharing information, for example, working with CFSAN on the issue of disease versus structure/function for drug/dietary supplement products. The division participates in many groups and committees such as: Health Fraud, Bovine Spongiform Encephalopathy, Botanicals, Internet and Homeopathy.

DRUG DIVERSION AND COUNTERFEIT DRUG PROGRAM

Introduction--Bogus and imitation drugs were recognized during the agency's early years as found in the Wiley Act of 1906. Also, the agency's involvement in counter diversion surveillance and prosecution dates from the 1950s. In 1951, the Durham-Humphrey Amendment aided this activity by defining prescription drugs and limiting their availability and distribution under state licensure. In that time, over two-thirds of the criminal actions initiated by the agency were based on the diversion of prescription drugs from licit channels of commerce. These black market channels often bypass the requirements that limit access to these drugs through a licensed pharmacy on the order of a licensed practitioner. Counterfeit drugs were not addressed until the Drug Abuse Control Amendments of 1965.

Counterfeit drugs are defined in the Act and may be found in either licit or illicit channels of commerce. Imitation drugs, also referenced in the Act, are defined by dictum and judicial decision. Bogus drugs may not conform to counterfeit or imitation parameters but do include other related drugs marketed under deceptive conditions with the intent to defraud.

Purpose--The purpose of the program is to direct the Center's compliance activities for drug diversions (not related to the Prescription Drug Marketing Act [PDMA]); counterfeit, imitation, and bogus drugs. The objectives of the program are as follow:

- Assure the security, identity and control over the distribution of drugs,
- Maintain close liaison with our international enforcement counterparts,
- Provide intelligence to and regulatory collaboration with other Federal agencies such as the Department of Justice, the Customs Service, the Drug Enforcement Administration, and the Federal Trade Commission, to complementary State authorities and criminal investigative components within the agency.

Program Description--Drugs are considered diverted when they move in commerce outside normal distribution channels. Manufacturing sources may be underground or not legally recognized by enforcement authorities. Drug diversion activities include black market sales associated with performance enhancing drugs such as anabolic steroids and schemes to bypass legitimate channels of distribution such as offshore pharmacies (foreign-based establishments that market unapproved drugs directly to the public). As international marketing barriers fall, the underground drug producers, and parallel and black market distributors become more pervasive and present an even greater challenge in our mission to safeguard the public health. The parallel market refers to distribution schemes for legally manufactured foreign drugs outside the intellectual property rights of the owner or diversion of domestically manufactured foreign versions of a drug.

Program Accomplishments--During fiscal year 1996, this program directed and guided evidence development and the selection of legal sanctions for twenty-four enforcement actions. Twelve cases for criminal litigation were supported, policies and strategies for sixteen initiatives were developed, and eight emerging diversion activities were identified and analyzed.

Compliance Activities--Scientific, technical and legal support consistent with criminal enforcement strategy resulted in the arrest and prosecution of those dealing with illicit bulk pharmaceutical chemicals, intermediate and finished drugs. Recent attention has been generated by the flood of imported unapproved drugs entering the country through offshore pharmacies and personal baggage. Often these drugs become street drugs of abuse, counterfeits, and drugs intended for parallel markets.

IMPORT/EXPORT PROGRAM

Introduction--The Import/Export Program underwent significant changes during fiscal year 1996. On April 26, 1996, President Clinton signed into law the FDA Export Reform and Enhancement Act of 1996 (EREA). The law allows the export/import of drug and biological products, whether or not approved in the United States, if the products are legally marketable in one listed country specified in the law.

One major provision of the new law requires the agency to issue certificates for devices and human and animal drugs within twenty days of receipt of the request. Prior law did not authorize the FDA to issue certificates, although the agency did so voluntarily.

Under the prior law, exports were limited to a list of 21 countries that required prior approval by the FDA. Extensive paperwork was designed to prevent transshipment, and the sponsor had to be actively seeking marketing approval. The new law expanded the list to 25 countries in which marketing authorization would be allowed,

and it required United States firms to notify the FDA before exporting. Additionally, provisions were added for countries requesting inclusion to the list and a petition procedure for the export of specific products to countries not on the list. Investigational products may be exported to a listed country without agency notification or approval, provided it meets Sections 801 or 802 of the Act.

Prior law prohibited the importation of products not in compliance with the new drug provisions of the Act. The new law allows the importation of a product not in compliance provided it will be used in a product that will ultimately meet compliance or export requirements. These product types include components of a drug or device, food or color additives, and dietary supplement ingredients.

Purpose--The Import/Export International Drug Team serves as the Center's focal point for compliance issues involving the import and export of pharmaceutical products. The program objectives are as follow:

- ♦ Facilitate trade between firms and foreign counterparts,
- ♦ Promote goodwill and cooperation between the United States and foreign governments through the Export Certificate Program,
- ♦ Assure the integrity of imported and exported drug products by monitoring investigational and unapproved new drugs.

Program Description--The FDA has historically issued different types of certificates, such as Certificates of Free Sale, Certificates for Export, Certificates to Foreign Governments and the European Union (EU) Health Certificate for Fishery Products. With expanding world trade, ongoing international harmonization initiatives, and developing international agreements, certificate requests for United States products are escalating. These export certificates are presently called Certificate to Foreign Government or Certificate of a Pharmaceutical Product. Certificates for products not authorized for sale in this country but that may be legally exported will be called Certificate of Exportability.

Requests for certificates must identify the products to be exported, certify that the firm and products are in compliance with the EREA, include a written statement verifying that the information in the request is true and accurate, and show the compliance status of the firm or product or both. Certificates are valid for 36 months from the date notarized. They are issued by the FDA for export purposes only and may not be used for domestic advertising. The requestor is notified that the issuance of a certificate will not preclude regulatory action, if warranted.

A new drug or antibiotic imported into the United States must either be the subject of an approved New Drug Application (NDA) or be a certified antibiotic. All imported OTC drugs must conform to each condition contained in Title 21, Code of Federal Regulations, Part 300 and in applicable monographs. Imported drugs must meet the same quality standards as those manufactured domestically. Additionally, overseas manufacturing facilities of imported drugs and drug substances must meet the same Current Good Manufacturing Practices (CGMP) as domestic facilities. All imported drugs must meet drug listing requirements, except those imported under the provisions for investigational use. The division assists field offices in monitoring the imported drug products program to ensure that importing firms meet the drug listing requirements. The import product listings are screened to prevent unapproved new drugs or misbranded drugs from entering the United States.

Program Accomplishments--During fiscal year 1996, because of the Export Certificate Program approximately 4,500 certificates (see chart page 49) issued to firms requesting exports to foreign countries. With the passing of the EREA, the mandated Export Certificate Program experienced extensive program analysis and revision.

A Memorandum of Understanding with the Russian Federation and the Republic of Belarus was enacted to expedite and facilitate the registration of United States products. Additional memoranda are being negotiated with the Ukraine and Armenia.

Compliance Activities--The division reviewed requests for Investigational New Drug exports in cooperation with the FDA's International Affairs Office. The division provided assistance and acted as liaison with foreign governments, agency field offices, and other Federal agencies to address issues such as the export of unapproved products related to the import and export of pharmaceutical products.

DRUG LISTING AND REGISTRATION COMPLIANCE PROGRAM

Introduction--The basis for the drug registration and listing system is the Drug Listing Act of 1972. All firms engaged in the manufacture, preparation, propagation, compounding, or processing of drugs or devices are required to register their establishments and to list all their commercially marketed drug or device products. The division manages the listing of all imported drug products. These products include prescription, over-the-counter, and homeopathic drugs and bulk drug substances. However, the division does not monitor the registration of foreign firms because they are not currently required to register with the agency.

The registration and listing of domestic firms are managed by the Product Information Management Branch in CDER's Office of Management, which includes technical data entry and database administration performed by a contract staff. The division conducts contract liaison activities. The registration and listing information obtained from government and contract sources is used by this program.

Purpose--The division directs all compliance activities related to listing of drug products and registration of the establishments provided for under the Drug Listing Act and related regulations. The registration and listing functions are as follows:

- Guide and interpret agency drug establishment registration and drug product listing regulations involving domestic and imported drug products,
- Serve as liaison with the Office of Compliance, contract staff and the Office of Management,
- Respond to requests from district offices to determine if the marketer of a detained product failed to list its products,
- Determine if compliance related issues require that a product be listed or a firm registered,
- Maintain hard copies of the listing and registration files,
- Determine the regulatory status of products.

Program Description--The division researches and answers inquiries from the drug industry concerning policy issues on registration and listing. This involves the interpretation of policy that may lead to the establishment of new policy because of ambiguous and unresolved questions.

The division determines the status of products on listing submissions from the regulated industry and determines if a specific product should be classified as a drug or device, a drug or food, or a drug or cosmetic. This is a complex issue and often involves jurisdictional determination between the agency's Centers before review of the product. Determining whether a product meets the definition of a drug is important. Relevant criteria include dosage form, potency, therapeutic claims, and the status of the specific OTC monograph.

Program Accomplishments--More than 200,000 records from the division's hard copy files of product listings and registrations of establishments were prepared for microfilming.

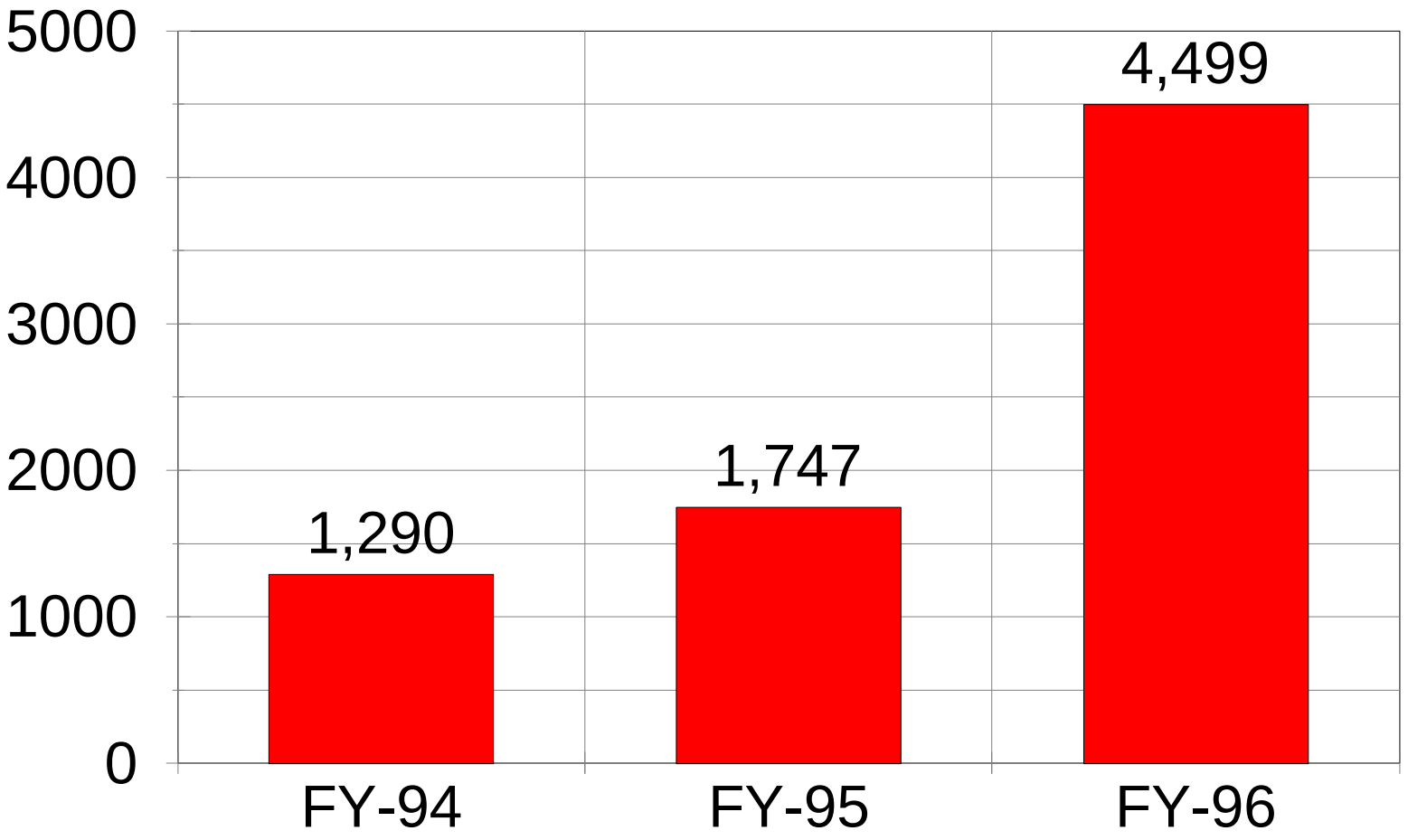
Since May 1996, the division issued untitled letters to 286 drug firms that failed to register their establishments, list their drug products, or correct their labeling. Labeling deficiencies include minor deletions to serious conditions that would warrant regulatory action. To date, 122 firms made corrections to comply with the regulations. As a result, the accuracy of the registration and product listing files will be improved.

For fiscal year 1996, the division listed 1,626 imported drug products of which 202 were detained by the field offices at the point of entry because they were unapproved new drugs or misbranded drugs. The division reviewed all of the products to ensure that they met drug listing requirements.

Compliance Activities--The division makes many policy and regulatory interpretations. Many jurisdictional determinations are required before a specific product can be classified as a drug or device, a drug or food, or a drug or cosmetic. They require a review of historical changes in status, agency policies, language used in the labeling, and interaction with other Centers. When the definition for a drug is met, the product will be listed in the drug listing database and the firm issued a label code as part of an NDC number.

Export Certificates Issued

Fiscal Year 1994 to 1996



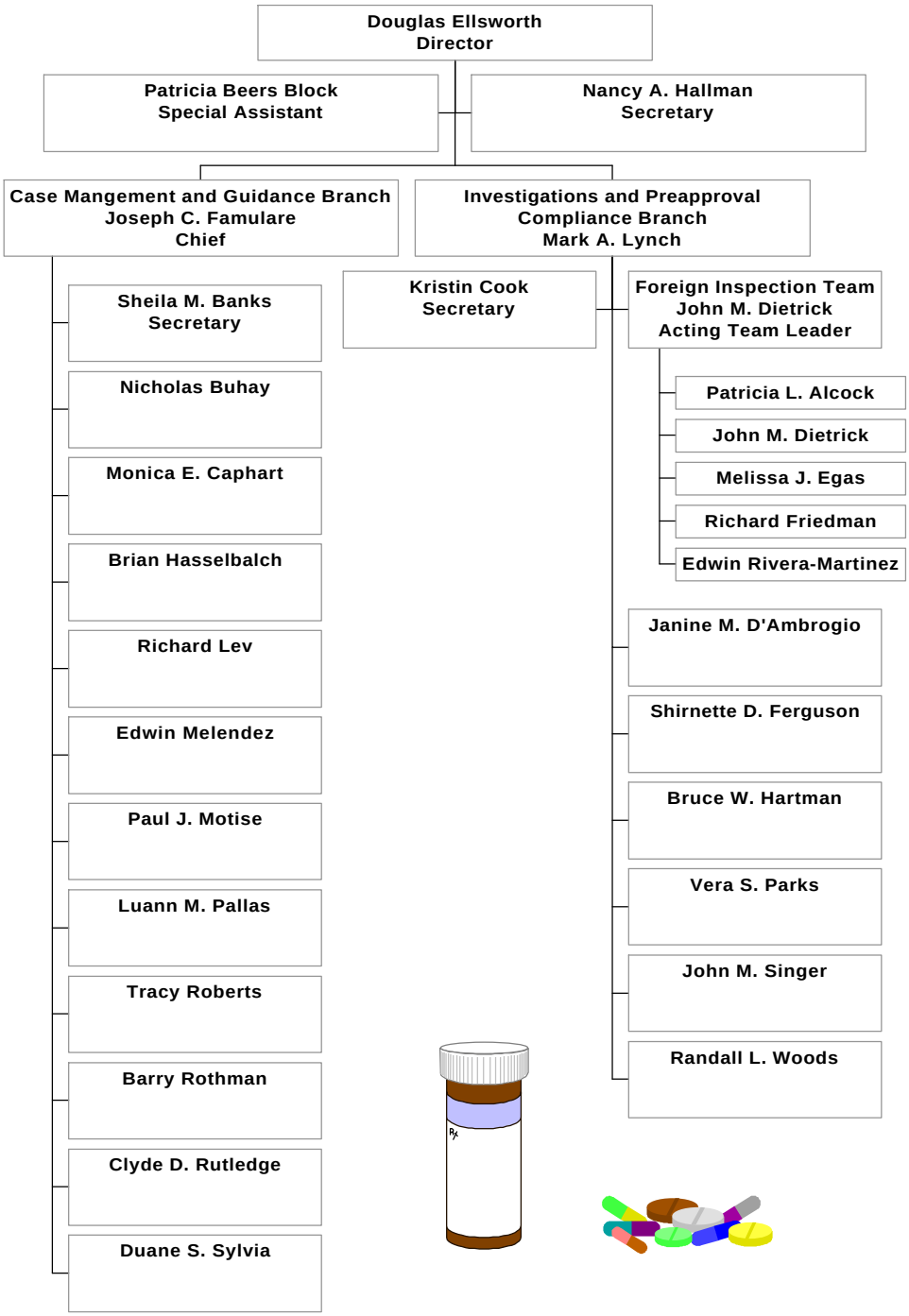
MANUFACTURING AND PRODUCT QUALITY

Doug Ellsworth
Director

The Division of Manufacturing and Product Quality consists of the Foreign Inspection Team, Case Management and Guidance Branch, and the Investigations and Preapproval Compliance Branch. The division is responsible for:

- Serving as the agency focal point for the interpretation and application of the Current Good Manufacturing Practice (CGMP) Regulations and provisions of the Federal Food, Drug, and Cosmetic Act (the Act) for human drug products,
- Developing and directing compliance policy and enforcement programs for product quality issues,
- Assuring the efficient and consistent handling of enforcement actions and providing litigation support,
- Developing guidance materials and educational programs to promote compliance with requirements of the Act and CGMP Regulations, and
- Managing the Preapproval Inspection Program and Drug Process Inspection Programs.

Division of Manufacturing and Product Quality



DIVISION OF MANUFACTURING AND PRODUCT QUALITY

MISSION STATEMENT

We serve the American public by:

- Assuring the quality and purity of marketed human drug products through enforcement of the Current Good Manufacturing Practice (CGMP) regulations for the manufacture, testing and holding of human drugs
- Providing clear and consistent guidance to the FDA field personnel, industry, and foreign governments on the production of safe and effective human drug products
- Assuring rapid access to quality new human drugs by verifying new drug application commitments, CGMP compliance, and submission of supporting data before and after application approval
- Ensuring that appropriate corrective action is taken when human drug products are unsafe, adulterated or manufactured out of conformance with application commitments

PREAPPROVAL INSPECTIONS/INVESTIGATIONS COMPLIANCE PROGRAM

Introduction--The Preapproval Inspections/Investigations Compliance Program assures that establishments involved in manufacturing, testing, or otherwise manipulating new drug dosage forms and substances are audited. These audits determine: (1) a firm's compliance with CGMPs, (2) a firm's adherence to application commitments, (3) the authenticity and accuracy of data, and (4) the adequacy of analytic methodology. The program defines the cooperative roles of district investigators and analysts, Center scientists and Office of Compliance staff in the preapproval process.

Purpose--The Center's role in the preapproval process is to review data submitted to the agency as part of premarket applications for new and generic drugs, establish specifications for the manufacture and control of the drug product based on submitted data. In addition, the CGMP compliance status of firms seeking certification or approval of drug products and drug substances is evaluated.

Program Description--The program represents the agency's strategy for assessing data and manufacturing processes used to support a new drug application. Before application approval, the FDA must determine if all establishments that will participate in the manufacture, packaging or testing of the finished dosage form or new drug substance are in compliance with CGMP and application commitments. This compliance evaluation is determined by conducting preapproval inspections (conducted by agency field personnel and/or trained and experienced Center personnel), and by evaluating firms' compliance histories. Preapproval inspection results are reported to the Office of Compliance for evaluation and further communication with the appropriate review division.

Based on the compliance evaluation, the division may recommend the approval or withholding of approval of an application, may request additional inspections, or may consider other regulatory and/or administrative action. The division provides case development support to investigator and analyst teams before and during inspections. Additional program responsibilities include developing enforcement strategies and initiatives, and preparing guidance documents.

Program Accomplishments--During fiscal year 1996, the division evaluated 1,426 foreign establishments and 3,010 domestic establishments (see chart page 67). These establishment evaluations supported Center review of 121 new drug applications and 214 abbreviated new drug applications. Division personnel participated in several training programs and industry workshops on the preapproval inspection program.

The division, in cooperation with other Center and agency components, is developing a draft guidance document that will articulate the agency's current opinion on how a firm should prepare for a preapproval inspection.

The division also supported the design and implementation of the Establishment Evaluation System (EES) pilot. This information technology initiative will provide a single management information system for preapproval compliance evaluations that can be used by district offices and Center units.

Compliance Activities--The division is responsible for monitoring the compliance status of the drug industry and issuing preapproval inspection assignments according to Center policy. When a preapproval inspection is not assigned, the appropriate districts are notified of applications under review for firms in their jurisdictional areas. Compliance evaluations are developed and problems communicated to the appropriate review division.

The division is the focal point for inspections of foreign drug firms and laboratories (see charts pages 69-79). Inspection requests are coordinated with other Center and agency components. Through review of inspection reports and evidence, the division evaluates compliance status, develops enforcement strategies, and takes appropriate administrative and regulatory action for foreign establishments.

The division also manages the preapproval inspection program for domestic drug firms. It conducts a wide range of activities to obtain information necessary to determine if drug manufacturers and drug products comply with applicable requirements of the law. Activities are coordinated between other Center and agency units. Through review of inspectional findings and other information, the CGMP compliance status of firms is evaluated. The division recommends administrative actions for drug product quality problems, and supports administrative action taken by other Center components

The division may request inspections of foreign and domestic establishments that intend to manufacture drugs when any of the following criteria apply:

- The drug has a narrow therapeutic range.
- The drug is a new chemical or molecular entity.
- The drug is a generic version of one of the 200 most-prescribed drugs.
- The drug will be manufactured in a facility where the current CGMP status for the dosage form type is not acceptable or is based on an inspection older than two years.

- ♦ The drug will be manufactured by an applicant who has never filed an NDA/ANDA in the past.
- ♦ The drug is the first generic version.
- ♦ Center review reveals discrepancies warranting investigation,
- ♦ The firm is a manufacturer of bulk pharmaceutical chemicals or an ancillary firm such as bulk substance sterilizers, labelers, packagers, testing laboratories, etc.

The division may request inspections of facilities that are new, have undergone major construction, or have new dosage form manufacturing processes as noted by an applicant's supplement. Application supplements are usually evaluated using the same criteria as original applications. New dosage form manufacturing facilities require product-specific inspections if the drug product fits any of the special criteria listed above.

The division provides case development support to field investigator and analyst teams before and during preapproval inspections. It determines the integrity of data submitted in new drug applications and applies the Application Integrity Policy when data integrity problems exist. Division personnel respond to many inquiries from firms and their agents requesting guidance on acceptable drug CGMPs. The division evaluates preconstruction facility submissions, supplies constructive comments and correctional guidance, and participates in educational programs to clarify agency preapproval issues.

DRUG PROCESS INSPECTION COMPLIANCE PROGRAMS

Introduction--A primary mission of the agency is comprehensive regulatory coverage of all aspects of drug product production and distribution to ensure that drug products meet the requirements of the Act and are consistently high in quality, and that the firm manufacturing, testing, repackaging, and/or processing the product is operating in a state of control. Evaluating the conditions under which drug products are manufactured, tested, packed and held is accomplished through on-site inspections.

Purpose--The Drug Process Inspection Compliance Programs assess the adequacy of CGMP regulations and guidelines and the agency's regulatory policies by gathering industry-wide data on changing practices and technology. Such data gathering is accomplished under these programs primarily through on-site inspections. On-site inspections also reduce consumer exposure to defective drug products by preventing the marketing of violative drugs or removing violative drugs from the marketplace.

Data acquired through on-site inspections reveal areas where increased educational efforts are needed. When problem areas are identified, the agency can heighten industry understanding of the regulations and policies governing GMP compliance by clarifying agency expectations of firms. This is accomplished through the development of guidance documents, revision of regulations, and participation in industry and agency seminars.

Program Description--Specialized compliance programs address the CGMP needs of unique drug products and processes. The programs determine the GMP compliance status of firms engaged in the manufacture, processing, holding and/or testing of pharmaceutical active ingredients and finished pharmaceutical drug products. The program objectives are accomplished through an inspectional stage, a review stage when inspectional findings are evaluated for significance, and a regulatory and/or administrative stage when deviations support voluntary, regulatory, or administrative action. These compliance programs include specific guidance for conducting inspections and suggestions for developing and handling voluntary, regulatory, and administrative actions.

Drug Process Inspection Compliance Program (General)

This program gives guidance for conducting inspections and procedures for determining if drug processes used by a firm are in a state of control. A drug firm is considered operating in a state of control when its manner of operation assures compliance with CGMP regulations. The result is the production of a finished drug product for which the quality, strength, and purity have been assured throughout production.

The adequacy of a firm's quality assurance systems is determined by conducting physical audits of these systems during on-site inspections, and then comparing the audit findings with the CGMP requirements.

A complete inspection of all systems and processes would normally include assessing the adequacy of:

- Buildings and equipment,
- Personnel training, qualifications, and experience,
- Components used to manufacture drug products,
- Manufacturing operations (including, for example, cleaning procedures and controls to prevent contamination),

- Laboratory controls,
- Packaging and labeling operations,
- Records and reports, and
- Validation.

Sterile Drug Process Inspection Compliance Program

The Sterile Drug Process Inspection Compliance Program is intended to cover the manufacture of all sterile drug products, including sterile bulk drugs, ophthalmic and otic dosage forms, and small and large volume parenteral products. This program provides guidance for conducting inspections of manufacturers of sterile bulk and finished dosage form drug products to determine compliance with the Act and the CGMPs. It gives guidance on the significance of inspectional findings and suggested remedies for ensuring that appropriate corrective action is taken by the industry (voluntary actions) or by the FDA (regulatory and/or administrative actions).

Drug Repackers and Relabelers Inspection Compliance Program

The Drug Repackers and Relabelers Inspection Compliance Program represents the agency's strategy for assessing drug repackaging and relabeling operations for compliance with the CGMPs and labeling requirements. This program covers:

- Firms that repackage solid and liquid bulk dosage forms into smaller packages,
- Firms that repackage from conveyances (such as, tank cars) into smaller containers (such as, drums),
- Contract packagers who package expressly for manufacturers of dosage forms,
- Repackagers or relabelers of antibiotics, and
- Shared services operations.

The program requires the review of a firm's quality assurance system(s) against CGMP requirements. Inspectional audits of these systems assess the adequacy of all significant drug repackaging and/or relabeling process and control systems used by firms. Most important, systems must prevent mix-ups of products or labeling.

Radioactive Drug Inspection Compliance Program

This program supplements the Drug Process Inspection Compliance Program by supplying specialized instructions for conducting inspections of radioactive drug manufacturing establishments. Radioactive drugs, including Positron Emission Tomography (PET) products, are regulated the same as other drug products. With the exception of some research uses, all radiopharmaceuticals are considered new drugs and subject to the applicable provisions of the Act and regulations. Radioactive drugs may be administered orally, by injection, or inhalation and may be either diagnostic or therapeutic. A diagnostic radioactive drug functions *in vivo* as a radioactive tracer. A therapeutic radioactive drug contains larger quantities of radioactivity for destruction of diseased cells or tissues.

Compressed Medical Gas Inspection Compliance Program

Compressed medical gases are prescription drugs administered to patients who are often unconscious or unstable. The methods of filling compressed medical gases into refillable high pressure cylinders or cryogenic vessels are unique in the drug industry. In addition, the container/closure systems used for medical gases are unlike those used for other drug products. Therefore, a set of strict prefill inspections is essential to ensure that the container/closure systems are acceptable.

Compressed medical gases must be manufactured, processed, filled and packaged using CGMPs. The objectives of this program are to:

- Assess the operations of the compressed medical gas industry to determine if they conform with CGMP regulations,
- Assure the quality of compressed medical gases through inspections, voluntary corrective action, and appropriate enforcement actions to achieve compliance with CGMP regulations,
- Identify practices that need correction or improvement(s), and
- Determine the need for specific CGMPs or revisions to guidelines for the

operations of the compressed medical gas industry.

Bulk Pharmaceutical Chemicals Inspection Compliance Program

The Bulk Pharmaceutical Chemicals Inspection Compliance Program focuses on the educational and inspectional aspects of regulating the bulk active pharmaceutical ingredient industry. Bulk active pharmaceutical ingredients are chemicals used in the manufacture of finished drug products. This program applies only to those bulk pharmaceutical chemicals (BPC) intended for use as active components of drug products. Although the CGMP regulations do not apply to bulk active pharmaceutical ingredients, they are subject to the broad requirement of the Act mandating that methods used in the manufacturing, processing, packing or holding of the drug must be in conformance with CGMP.

Program Accomplishments--Significant advances were made in developing guidance to industry and field offices, and participating in industry and field training programs and workshops, particularly in the compressed medical gas area. Eight medical gas workshops were held throughout the country. Because of the success of the workshops conducted in the Florida District, a division employee and the Florida District Office received Vice President Gore's Golden Hammer Award. Enforcement actions to achieve compliance in the medical gas area included the issuance of warning letters, the approval of seizures and an injunction of a firm implicated in the deaths at a Texas VA hospital due to carbon tetrachloride contamination.

This division continues to play a role in promulgating a precedent-setting regulation on electronic records and electronic signatures. The rule covers all the FDA's programs and allows the agency to accept (under certain circumstances) electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper.

Refinement of several guidance documents continued throughout fiscal year 1996. A draft guidance document entitled "Guidance for Industry: Manufacture, Processing or Holding of Active Pharmaceutical Ingredients" was released to trade and scientific associations and widely distributed to interested parties domestically and abroad. This document was posted on the CDER Internet HomePage for comment.

Compliance Activities--For each of these programs, the division identifies the need for specific CGMPs and, as appropriate, develops revisions of current CGMPs, and guidance and policy documents to express the Center's current interpretation and application of the CGMP regulations. The division serves as the Center focal point for uniform interpretation of the law and regulations governing drug product quality, gives oral and written guidance to both the field and industry, and evaluates the effectiveness of compliance and educational programs. In addition, the division identifies trends, develops enforcement strategies, provides case development support to investigators

and analyst teams, and processes legal and administrative action recommendations.

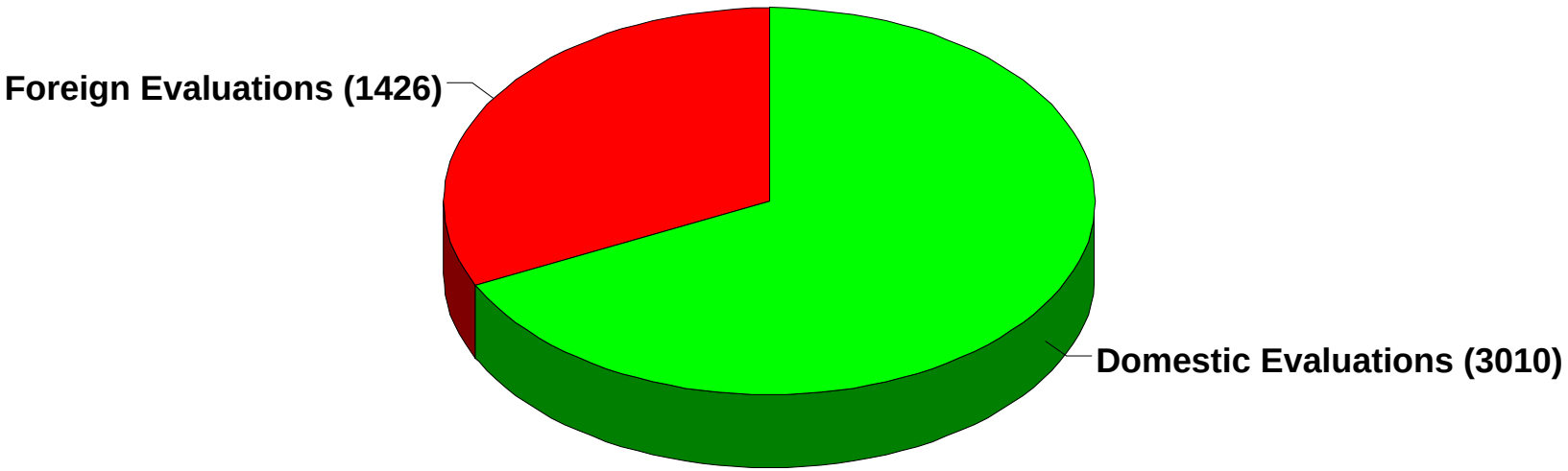
The division responds to inquiries from the regulated industry, consumer groups, and regulatory officials concerning the interpretation of drug product manufacturing regulations and guidelines. It evaluates and develops responses to public comments submitted in response to *Federal Register* statements, guidelines and citizen petitions on CGMP issues. This division actively supports educational activities by participating in workshops, video conferencing, and meetings with industry.

The division provided extensive guidance and support for several international negotiations involving memoranda of understanding or mutual recognition agreements on pharmaceutical CGMP inspections. Other activities, such as developing guidance documents, updating regulations, conducting site reviews, responding to inquiries, and participating in industry and agency seminars, increase the division's ability to ensure that firms understand the agency’s current interpretation and application of CGMP regulations and statutory requirements.

Establishments Evaluated

Supporting NDAs and ANDAs

Fiscal Year 1996



Total Establishments Evaluated 4436

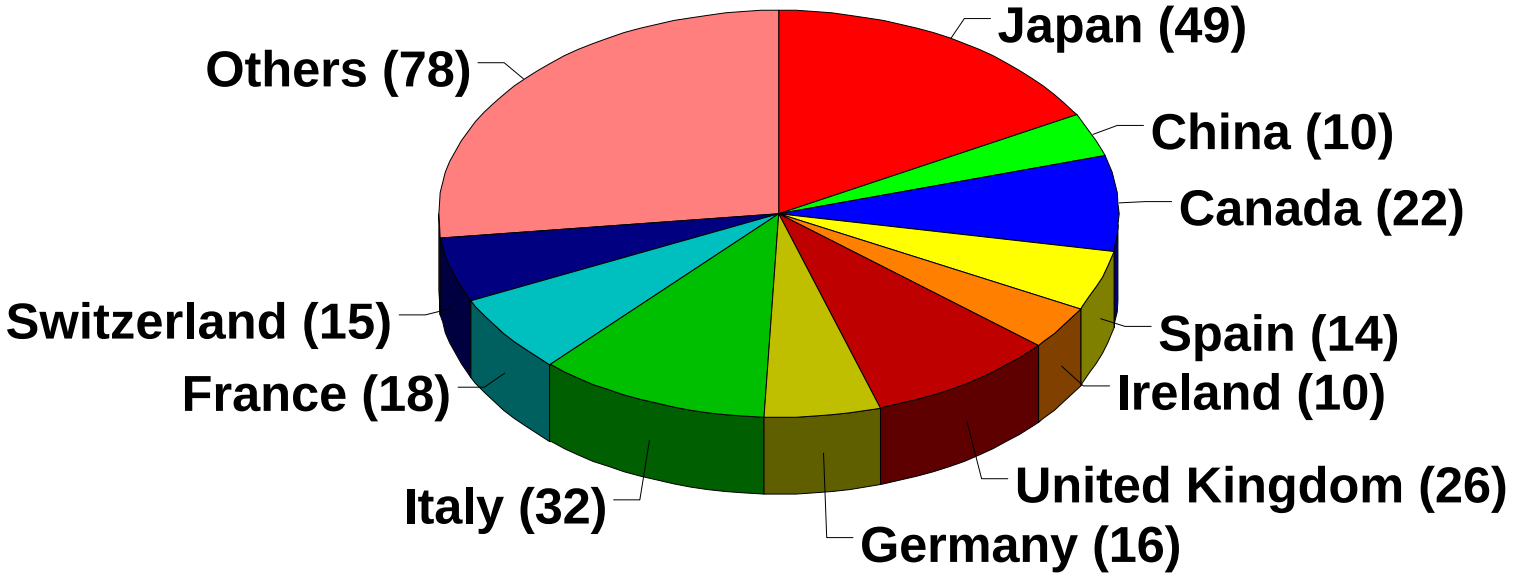
Types of Foreign Establishments Inspected

Firm Type	FY 95	FY 96
Active Pharmaceutical Ingredient (API) Manufacturers	173	183
Finished Dosage Manufacturers	75	74
API and Finished Dosage Manufactures	10	11
Contract Labs	12	16
Contract Micronizers	4	1
Contract Sterilizers	1	0
Drug Repackers	3	4
Pharmaceutical Warehouses	0	1
Total Inspections	278	290

Foreign Inspections

By Country

Fiscal Year 1996

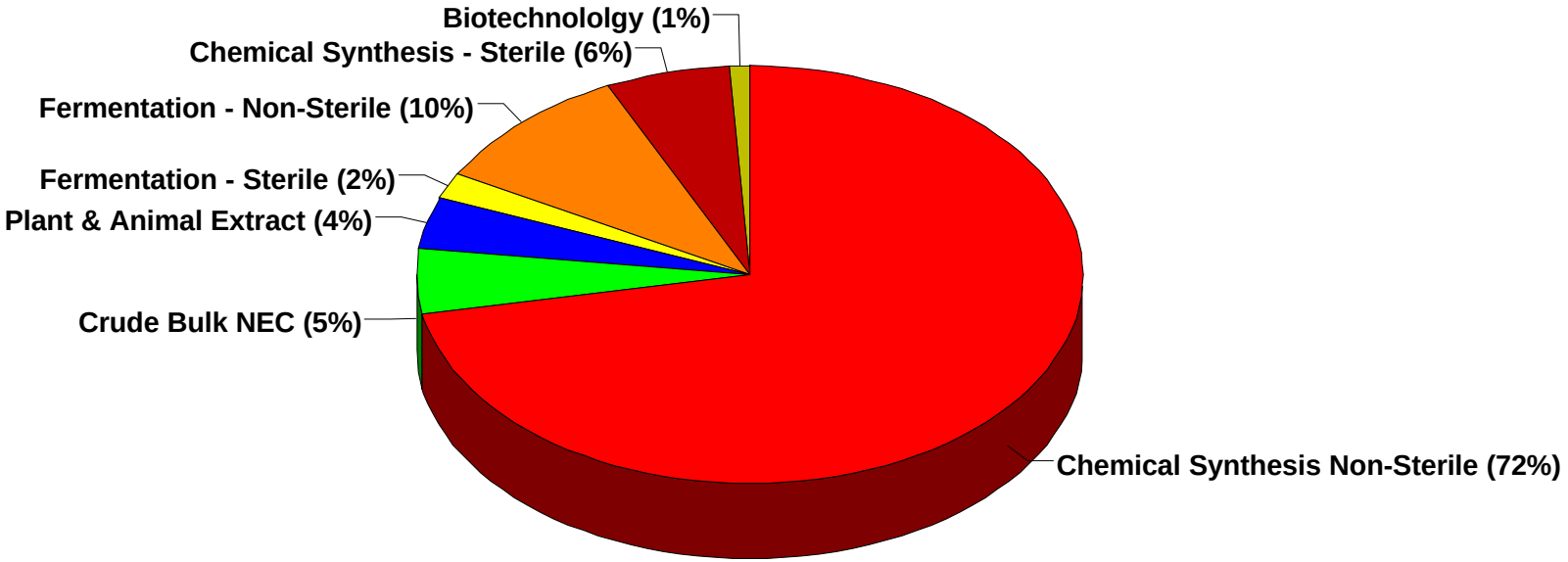


Total: 290

Active Pharmaceutical Ingredient

Manufacturing Processes Inspected

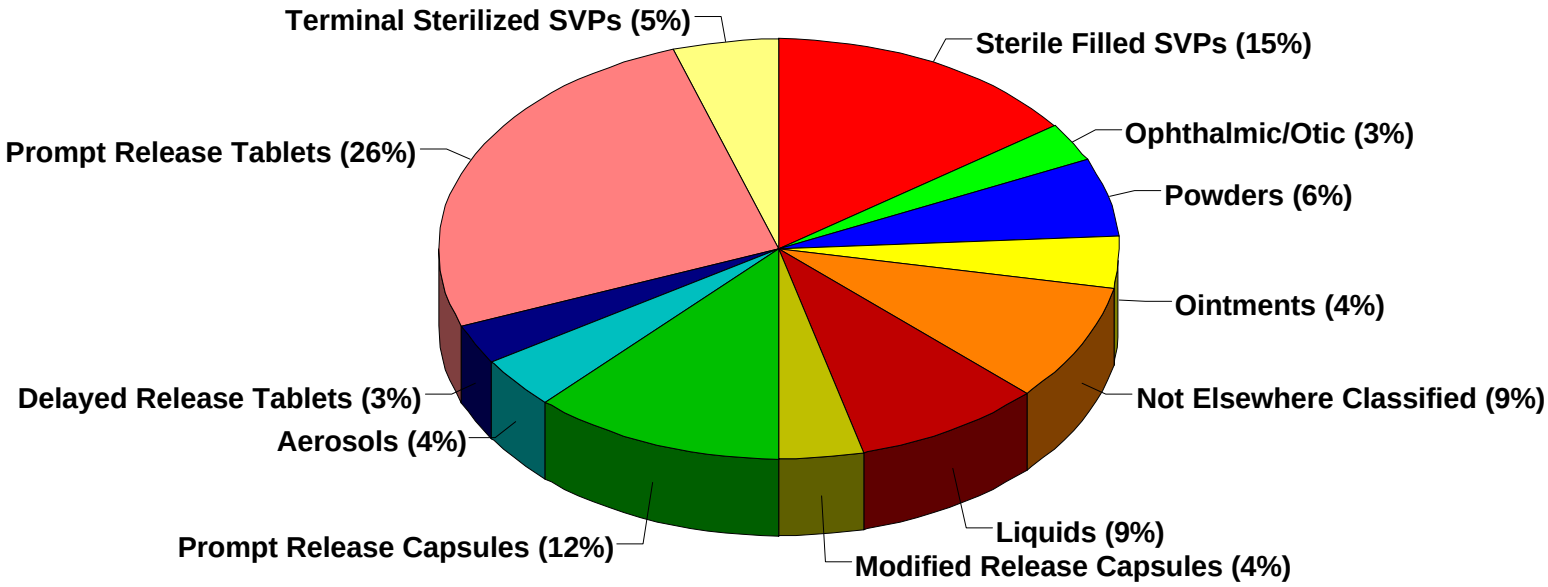
Foreign



Finished Dosage Manufacturing

Processes Inspected

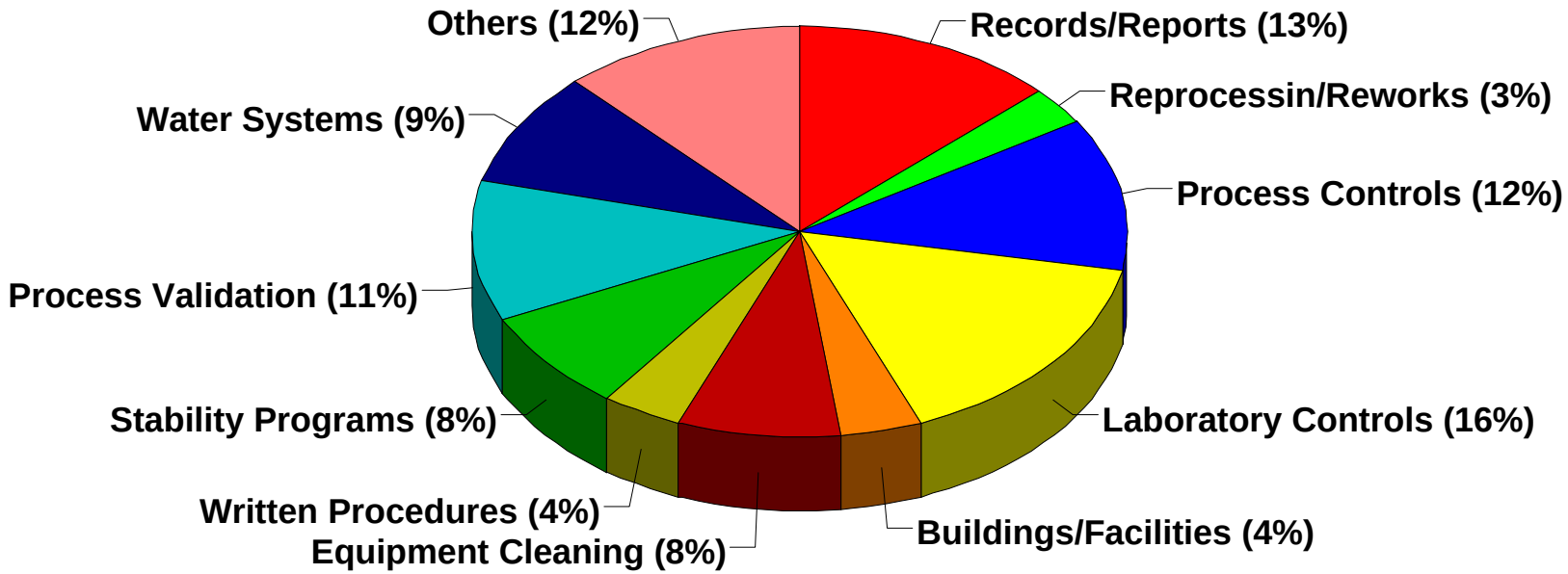
Foreign



Current Good Manufacturing Practice

Deficiencies at API Manufacturers

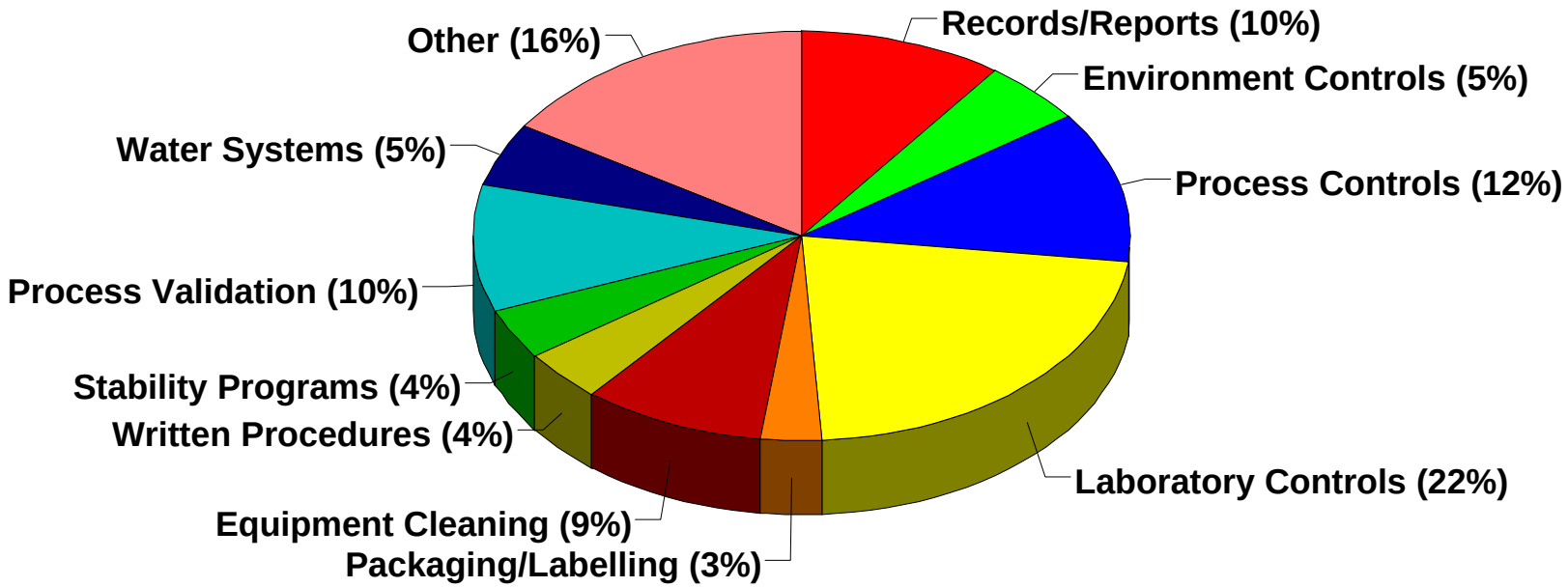
Foreign



Current Good Manufacturing Practice

Deficiencies at Dosage Manufacturers

Foreign



PRESCRIPTION DRUG COMPLIANCE AND SURVEILLANCE

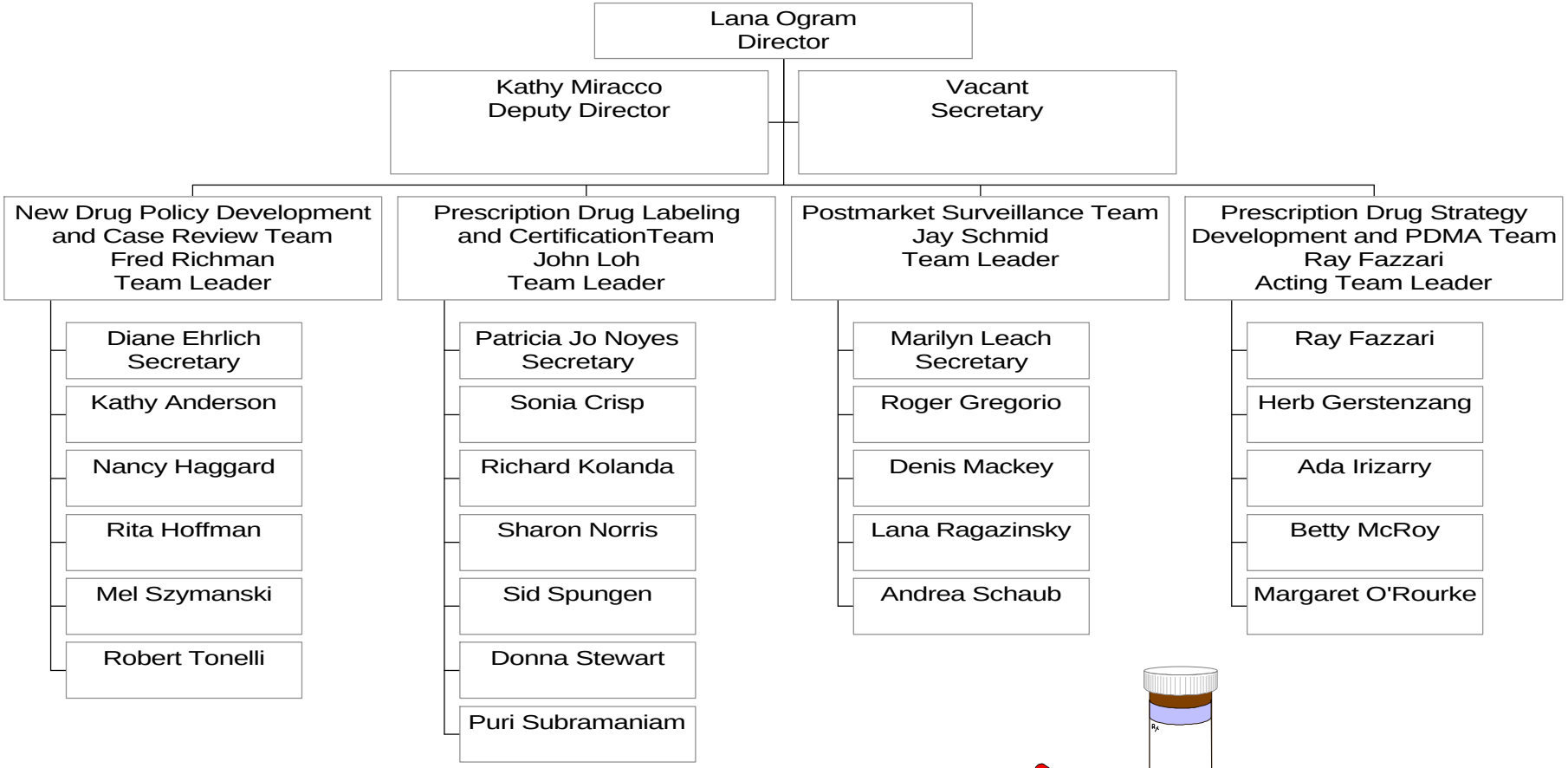
Lana Ogram
Director

Kathy P. Miracco
Deputy

The Division of Prescription Drug Compliance and Surveillance is operating under a pilot reorganization consisting of four Teams: Postmarket Surveillance, Prescription Drug Labeling and Certification, Prescription Drug Strategy Development and PDMA, and New Drug Policy Development and Case Review. The division's primary responsibilities include enforcing the new drug and misbranding provisions of the Food, Drug, and Cosmetic Act (the Act) for prescription drug products, and monitoring the quality of the nation's drug supply through postmarketing surveillance activities. Program areas include the following:

- Drug Efficacy Study Implementation
- New Drugs (Prescription) - Not Covered by Approved NDAs
- Drug Experience Reporting
- Drug Product Surveillance
- Drug Listing - Labeling Review
- Drug Quality Reporting System and NDA Field Alert Reporting
- Prescription Drug Marketing Act

Division of Prescription Drug Compliance and Surveillance



DIVISION OF PRESCRIPTION DRUG COMPLIANCE AND SURVEILLANCE

MISSION STATEMENT

We serve the American people by:

- Developing policies and compliance strategies to ensure that marketed prescription drug products are safe and effective for their intended uses and are properly and legally labeled
- Supporting the operation of the Health Care Financing Administration (HCFA) and the Drug Rebate and Drug Reimbursement Programs by identifying less-than-effective products
- Monitoring the quality of the nation's drug supply through postmarketing surveillance and product testing
- Identifying health hazards associated with the manufacturing, labeling and packaging of pharmaceuticals through the Drug Quality Reporting System, Field Alert Reports, and Adverse Drug Experience reports, and removing unsafe and ineffective products from the marketplace
- Resolving reported medication errors for drugs not covered by approved new drug applications
- Determining the effectiveness of tamper-resistant packaging (TRP) features to reduce the likelihood of successful tampering with the over-the-counter drug supply
- Preventing the diversion of counterfeit, subpotent, adulterated, and misbranded prescription drug products by administering the Prescription Drug Marketing Act
- Assuring the quality of insulin products and oral digoxin tablets before marketing through certification programs

NEW DRUG PROGRAM AREAS

Marketed Prescription Drugs Without Approved Applications

Introduction--The Food, Drug and Cosmetic Act of 1938 requires that new drugs be reviewed and approved for safety before marketing. Efficacy was added to this requirement with the enactment of the 1962 amendments to the Act. However, several drug categories have not been approved for safety and/or efficacy. These categories include drug products (1) pending the Drug Efficacy Study Implementation (DESI) review, (2) identical to pre-1962 products not approved for safety, (3) not identical to pre-1962 products not approved for safety, and (4) identical, related, and similar to products approved for safety and efficacy.

Purpose--The purpose of this program area is to identify the compliance status of all currently marketed drugs and take appropriate action to assure the safety and effectiveness of the nation's drug supply.

Program Description--Drugs that require approved applications are identified through review and categorization of products in the drug listing database. These products are coded into the four categories mentioned in the introduction.

Program Accomplishments--Approximately 6,000 unapproved drug products were reviewed and categorized.

Compliance Activities--The division issued untitled letters to two firms notifying them of their products' new drug status. Thirteen compliance action recommendations were received involving new drug charges. Review of the recommendations resulted in processing four warning letters, one seizure, and two injunctions. Two injunctions and four warning letter recommendations are under review. The division is providing guidance in support of a case against an individual charged with criminal contempt, mail fraud, and introducing unapproved new drugs into interstate commerce. In addition, this division assists the regulated industry by responding to inquiries regarding the status of proposed products intended for marketing.

FDA/Health Care Financing Administration (HCFA) Agreement

Introduction--In 1992, the FDA/HCFA Agreement was developed to support HCFA's two national health care programs: the Drug Rebate Program and the Drug Reimbursement Program.

Purpose--First established in 1981, this program ensures that drug products available to Medicaid patients are effective, and Federal funds are not allocated for less-than-effective drugs. The Medicaid Drug Program is supplemented through the Drug Rebate Program, under which firms reimburse the State part of the cost of drugs dispensed under State programs.

Program Description--HCFA relies on the division to determine the effectiveness status for marketed drug products because less-than-effective drugs are not eligible for reimbursement by HCFA. The division updates the list of non-reimbursable drugs quarterly and gives this information to HCFA upon completion and as information becomes available.

Program Accomplishments--The division prepared reports for HCFA's programs and the DESI less-than-effective drug products for the Inspector General's office. The division interpreted policy and gave guidance on HCFA-related issues, unapproved marketed drugs, DESI, and drug listing to Federal and local government agencies, State Medicaid offices, third party drug plans, pharmacists, drug manufacturers, distributors, and private database firms. The government saved money and patients received effective drugs because of our activity in this area.

Manufacturing Pharmacies

Introduction--The nation's health care delivery system is undergoing change to increase efficiency while keeping costs down. Some changes are affecting prescription drug manufacturing and delivery systems and relate directly to the agency's regulation of drug products. Changes from traditional drug delivery at the dispensing level include state-licensed pharmacies that prepare their own versions of commercially available drug products and firms that offer contract preparation services for sterile products.

Purpose--The purpose of this program is to evaluate the applicability of and give guidance on the Act's requirements and regulations as they pertain to prescription drug product preparation/manipulation by state-licensed pharmacies engaged in traditional, extemporaneous compounding and those engaged in drug manufacturing.

Program Description--The division is assessing policy issues involving the preparation/manipulation of prescription drug products by state-licensed pharmacies engaged in traditional, extemporaneous compounding and those engaged in drug manufacturing.

Program Accomplishments--During fiscal year 1996, the division convened and chaired a task force to evaluate the terms, requirements, and options concerning pharmacy compounding and manufacturing. The division prepared an assessment of program areas, briefed Center management and developed a framework for future legislative initiatives. The division participated in inspections of two firms that prepare sterile intravenous admixture drugs.

Compliance Activities--During fiscal year 1996, the division received six regulatory action recommendations. Two warning letter recommendations and one injunction were processed, and recommendations for two warning letters and one seizure are under review.

Jurisdictional Reviews

Introduction--In 1991, Intercenter Agreements were established between the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, and the Center for Biologics Evaluation and Research. The agreements determine when a product is regulated as a device, drug, biologic, or combination thereof.

Purpose--The purpose of this program area is to decide primary Center jurisdiction for both the premarket and postapproval review and regulation of FDA-regulated products.

Program Description--The Centers coordinate their activities to ensure that products are reviewed by the appropriate Center(s). Manufacturers' product designation requests are reviewed to decide primary jurisdiction over products that combine elements regulated by more than one Center, or where the responsibility for the product is unclear or in dispute.

Program Accomplishments--During fiscal year 1996, thirteen requests for designation were completed.

Compliance Activities--The division furnished guidance and policy interpretation on jurisdictional reviews to industry and other agency units.

PRESCRIPTION DRUG LABELING REVIEWS

Introduction--The division ensures that marketed drug products are properly and legally labeled. Drug product labels are reviewed by the Office of Management before entering a drug product into the Drug Listing Database. Labels that do not meet drug labeling regulations are referred to this division for review and appropriate action.

Purpose--Patients are assured appropriate treatment when a drug product is properly labeled and a physician is fully informed about the product.

Program Description--Descriptive information from product labels, referred to the division by the Office of Management, is placed into a database. Labels are reviewed for compliance with applicable regulations.

Program Accomplishments--The division answered many requests from industry on drug products' marketing and labeling compliance status. A systematic approach to label review and resolution of identified problems is under development.

Compliance Activities--Misbranded drug products without adequate directions for use were destroyed because of approval of a seizure recommendation. An injunction that included misbranding charges was processed, and the firm ceased distribution of the product. One warning letter was processed, and two injunctions that include both misbranding and new drug charges are under review.

POSTMARKETING SURVEILLANCE PROGRAMS

Drug Quality Reporting System (DQRS)

Introduction--Since the early 1970s, the agency has operated a program directed to health care professionals for voluntary reporting of observed or suspected defects and quality problems associated with marketed drug products. Reports are received through the agency's MedWatch Program and the United States Pharmacopeia's (USP) Drug Product Problem Reporting system. The reports are reviewed to identify potential health hazards, determine industry trends, and develop special programs and surveys.

Purpose--This program identifies significant health hazards associated with pharmaceutical manufacturing, packaging, and labeling, and maintains a central reporting system for detecting problem areas or trends requiring compliance action.

Program Description--The division evaluates and sets priorities for drug quality reports submitted through the MedWatch and USP Programs. Field investigative assignments are developed and monitored, and inspection reports and analytical results are reviewed for trend analyses. The division shares the data with the USP to enhance compendial standards for drug products. Reports of bioequivalence problems and resultant follow-up actions are forwarded to the Therapeutic Inequivalence Action Coordinating Committee for review. The division consults with the Division of Medical Products Quality Assurance on drug quality problems or adverse reaction reports received through the Government-Wide Quality Assurance Program.

Program Accomplishments--During fiscal year 1996, 3,232 reports (see chart page 101) were reviewed.

Compliance Activities--Ten products were recalled and forty-one voluntary corrective actions were achieved.

Drug Product Surveillance

Introduction--The division monitors the quality of the nation's drug supply through postmarketing surveillance sampling of foreign and domestic finished dosage forms and bulk pharmaceutical chemicals. Samples of selected drug products are tested for conformance with their respective analytical specifications.

Because many active ingredients are obtained from foreign sources and have not been subjected to structured analytical surveillance programs, foreign-source bulk pharmaceutical chemicals and finished dosage forms were added to the sampling program. The sampling of foreign-source products during domestic sample collections and at entry points has begun under this program.

Purpose--The Postmarketing Sampling Program determines the quality of the nation's drug supply and provides industry-wide statistical comparisons. Investigational and compliance efforts are directed toward drug products or manufacturers that represent a risk to the consumer.

Program Description--Sampling is accomplished through two types of surveys:

- Continuous surveillance for insulin, bioassay, and radioactive drugs--These surveys cover drugs that require continuous surveillance by agency policy or because they are difficult to manufacture, have narrow therapeutic ranges, low concentrations of active ingredients, or have other problems such as bioavailability.

- Periodic surveillance--These surveys are used for selected drug products annually and are designed to identify emerging problems. Product selection for these surveys is a coordinated effort between the Office of Compliance and the Center's review divisions. Selection is based on therapeutic significance, emerging problems, previous drug survey results, and economic importance.

Sample analyses are conducted by the agency's field and headquarters laboratories. Samples that do not meet their analytical specifications are referred to the district offices for investigational follow-up and corrective action.

Program Accomplishments--During fiscal year 1996, periodic surveys covering 56 drug products issued. Sample collection and analyses are in process.

Summary Reports were prepared for 34 of the 53 periodic surveys issued during fiscal year 1995. The 34 evaluations represent 427 finished dosage form samples for 42 drug products. Initial analyses revealed that seven samples of metered dose inhalation drugs did not meet their required specifications; however, sufficient sample size was not available for check analyses. Attempts to collect additional samples of the subject lots revealed the lots were no longer available; therefore, the analytical results are inconclusive. The product will be sampled and analyzed under special assignment. The remaining fiscal year 1995 survey evaluations have not been completed because sampling is ongoing.

All 180 bulk pharmaceutical chemical samples collected during fiscal year 1995 were analyzed and met their respective quality specifications (57 of the bulk samples were foreign-source products). In addition, 220 bulk pharmaceutical chemical samples (104 domestic and 116 foreign-source) were collected for forensic analysis. Forensic analyses were completed for 104 of the samples collected.

Five radiopharmaceutical products were collected and analyzed, and 28 drug products were sampled for bioassay surveillance. All samples met their respective specifications.

Approximately 200 postmarketing insulin samples are collected annually for surveillance testing by the agency's insulin laboratory. All samples met required specifications. The laboratory also performs ad hoc testing of insulin samples related to consumer complaints and reports of adverse reactions.

The division's postmarket surveillance initiatives were presented to (1) the Malaysian Ministry of Health during their National Pharmaceutical Control Bureau meeting, (2) the Canada-United States-Mexico Compliance Information Group, and (3) the Kingdom of Saudi Arabia.

Compliance Activities--Compliance follow-up was conducted for two products surveyed during fiscal year 1994--one was a calcium channel blocker and the other was a coronary vasodilator. Because of one sample failing dissolution requirements, a seizure recommendation was approved, and the manufacturer destroyed the product and ceased manufacturing. Twelve samples of another product manufactured by two firms failed dissolution requirements, and the firms are correcting the problem by revising their manufacturing processes.

Medication Errors Response Working Group

Introduction--Medication errors are caused by a variety of factors and can occur anywhere in the distribution system. Some common causes of medication errors include the following: poor communication, ambiguities in product names and directions for use, misunderstood medical abbreviations or writing, poor procedures and techniques, patient misuse, lack of product knowledge or training, and similar product labeling and packaging. In 1992, the Center's Medication Errors Subcommittee was formed to evaluate reports of medication errors received through the United States Pharmacopeia's Medication Errors Reporting System and the agency's MedWatch Program.

Purpose--The Medication Errors Response Working Group (MERWG) was implemented to evaluate and resolve reported medication errors for drugs not covered by approved new drug applications. Reports for approved drug products are forwarded to the agency's drug review divisions.

Program Description--MERWG develops initiatives to resolve medication errors that include: problems in labeling, packaging, manufacturing, similarly pronounced drug names, and drug nomenclature problems. This division evaluates reports received for prescription drug products not covered by approved applications. To resolve current problems and prevent future errors, product manufacturers are contacted to implement the necessary corrective actions, such as, labeling revisions or packaging changes. This division serves as liaison for reports forwarded to other divisions for review (i.e., nonprescription drug products).

Program Accomplishments--During fiscal year 1996, thirty-one medication error reports were evaluated for correction and/or resolution of problems with labeling or packaging for prescription and nonprescription drug products. Fifteen have been resolved, two were forwarded outside the Center, and fourteen are pending final resolution.

Compliance Activities--Improved drug package labels and product labeling resulted from communication with the responsible firms. The improved labels express information consistent with the products' label claims and in accordance with the agency's regulations. These improvements will reduce the likelihood of medication errors caused by health care professionals, reduce potential adverse drug reactions, and improve patient safety.

The division participated in meetings with the European Medicine Evaluation Authority, the Health Industry Manufacturers Association, and the Society of Hospital Pharmacists. The meetings focused attention on medication errors within the health professions and methods to prevent errors and improve reporting strategies.

Adverse Drug Experience Reports

Introduction--The agency's Adverse Drug Experience Program was established to monitor the safety of marketed drugs and to signal potentially serious, previously unexpected safety problems.

Purpose--The purpose of the program is to ensure that postmarket adverse drug experience (PADE) reports are submitted to the agency in accordance with the reporting requirements.

Program Description--PADE reports for domestic and foreign-source drug products are submitted to the agency by drug manufacturers, health care professionals, and consumers. The division develops, issues, and monitors field assignments for inspection of drug manufacturers who have submitted incomplete or late PADE reports. Compliance policy guidance and interpretation are given to the field investigators on the PADE regulations.

Program Accomplishments--During fiscal year 1996, ten inspections were conducted, and ten inspection reports were reviewed. The division is participating in revision of the Adverse Drug Experience Reporting regulations. The revision will harmonize the existing regulations with the International Conference on Harmonization (ICH) guidelines for reporting adverse drug reactions.

Compliance Activities--One warning letter issued citing violations with adverse drug experience reporting regulations.

New Drug Application (NDA) Field Alert Reports

Introduction--Since 1985, holders of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) have been required to submit Field Alert Reports to jurisdictional FDA district offices. The reports contain information about their distributed drug products and must be submitted within three working days of receipt by the applicant. Required information includes the following: any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; any bacterial contamination; any significant chemical, physical, or other change; deterioration in the distributed drug product; and any failure of one or more distributed batches of the drug product to meet the specifications established in its application.

Purpose--The program's purpose is prompt agency notification of significant problems that represent potential safety hazards for marketed drug products.

Program Description--District offices evaluate the field alert reports and conduct investigational follow-up. Copies of the reports and investigational findings are sent to the division for review. If a significant problem exists, the reports are forwarded to other divisions within the Office of Compliance to determine deviations from good manufacturing practices and the need to begin corrective action.

The division is responsible for assuring that applicants follow the timely reporting requirements for NDA/ANDA Field Alert Reports and for review and approval of regulatory actions for failure to meet these requirements.

Program Accomplishments--The division reviewed 200 NDA field alert reports.

Compliance Activities-- During fiscal year 1996, thirty-three drug products were recalled because of NDA field alerts.

TAMPER-RESISTANT PACKAGING REQUIREMENTS

Introduction--The regulations requiring tamper-resistant packaging (TRP) for certain over-the-counter (OTC) drug, device, and cosmetic products were published in the *Federal Register* in 1982. They were initiated following the Tylenol capsule tampering incident that resulted in seven deaths in Chicago during the fall of 1982.

The TRP regulations require that OTC human drug products (except dermatologicals, dentifrices, or insulin products), cosmetic liquid oral hygiene products and vaginal products, and contact lens solutions and tablets used to make these solutions for retail sale be packaged in tamper-resistant packaging.

Since 1982 the regulations were amended to:

- Exempt all lozenge products from both the packaging and labeling requirements,

- Exempt ammonia inhalants in crushable glass ampules, aerosol products, and compressed medical oxygen from the labeling requirements, and

- Require that unsealed two-piece, hard gelatin capsule dosage forms use a minimum of two TRP features in their packaging systems.

Purpose--The purpose of tamper-resistant packaging is to reduce the likelihood of successful tampering with affected products when they are accessible to the public (usually on a retail shelf), and to provide visible evidence to consumers when tampering has occurred.

Program Description--The division is the Center's tampering coordination unit for reports of alleged or confirmed tampering with drug products. It is responsible for determining the effectiveness and compliance status of (1) marketed OTC drug products with the requirements of the TRP regulations, (2) remedial packaging efforts to achieve appropriate correction because of regulatory action, and (3) innovative premarketing package designs. Special field surveys are planned and directed and compliance policy guidance is given to field offices. Regulatory actions are recommended and approved.

Program Accomplishments--During fiscal year 1996, thirty samples were evaluated for compliance with the TRP requirements. The samples represent four regulatory samples, twenty-five remedial samples, and one premarket innovative package design.

The division reviewed and gave comments on the draft Amendments to the TRP Requirements--Final Rule. Several briefing papers were prepared and many requests for policy interpretation and guidance were furnished to foreign officials, the pharmaceutical industry, professional trade associations, academia, packaging groups, consumers, inventors, and agency staff.

Compliance Activities--A foreign firm's product line was detained and refused entry for lack of compliance with the TRP requirements. Through communication with the firm and evaluation of sixteen samples of their remedial packaging designs, the firm's product line is now in compliance with the TRP requirements.

Review and evaluation of nine remedial samples resulted in three domestic firms bringing their products into complete compliance with the TRP requirements. The firms received warning letters for failure to comply with the TRP requirements last fiscal year.

PRESCRIPTION DRUG MARKETING ACT (PDMA)

Introduction--The Prescription Drug Marketing Act was enacted in 1988 after two years of Congressional investigations and hearings found widespread diversion of prescription drug samples, irregularities in the import and export of prescription drugs identified as American Goods Returned, and diversion of retail prescription drug stock through the secondary wholesaler network. The diversion of prescription drug products presented serious public health safety concerns because counterfeit, subpotent, adulterated, and misbranded drugs were being distributed without regard for the quality or source of the drugs.

Purpose--The purpose of the PDMA is to protect consumer health by preventing the diversion of counterfeit, subpotent, adulterated, and misbranded prescription drug products into the national distribution system.

Program Description--The division is responsible for the development and implementation of PDMA policy and enforcement strategies. This includes initiation of investigational assignments; review and approval of regulatory actions; litigation support; and preparation of advisory opinions and guidance to the regulated industry, health care professionals, Federal, State, and local regulatory agencies, and consumers. The division maintains the agency's PDMA database, which contains required industry reports of loss, theft, and alleged drug diversion. Reports of drug diversion or other criminal activity are forwarded to the Office of Criminal Investigations.

Program Accomplishments--During fiscal year 1996, the division reviewed 474 loss and theft reports, one report of American goods returned, and 38 drug diversion reports (see chart page 103). To promote compliance with the PDMA requirements, meetings were held with trade associations representing pharmaceutical manufacturers and distributors, the common carrier industry, pharmacy interns, and the CDER Stability Committee.

Compliance Activities--The draft regulation, Prescription Drugs, Policies, Requirements and Administrative Procedures; Final Rule, implementing the PDMA was reviewed and revised by the division. A warning letter was issued to a pharmacy for dispensing a sample product in a retail prescription. The pharmacy made corrective action to prevent recurrence of the PDMA violation. The division assisted the Office of Criminal Investigations in a criminal case against a retailer for wholesale distribution of prescription drugs without a state license. The individual was convicted. An investigation of a licensed wholesaler was conducted after the Centers for Disease Control reported serious illness linked to the firm's products. The investigation resulted in the recall of 53 lots.

CERTIFICATION PROGRAMS

Insulin

Introduction--The Act requires that batches of insulin be certified to ensure that they conform to standards of identity, strength, quality, and purity. Approved New Drug Applications are required for insulin products before certification.

Purpose--The certification program protects consumer health by assuring the quality of insulin products in distribution.

Program Description--The division issues insulin certificates and releases. Requests for certification are sent by the product manufacturers concurrently to the division and the agency's insulin testing laboratory. The division determines which batches will be tested and notifies the laboratory. Certification of master lots of insulin crystals (bulk batches) is a prerequisite to certification of finished dosage form batches. Under the current selective testing policy approximately one-third of the batches submitted for certification are tested. The analytical data submitted with the request for certification and agency laboratory results, if any, are reviewed. Batches are released or certificates are issued for those batches determined to meet the requirements. A certification fee schedule has been established by the Act. The agency's Accounting Branch manages the insulin certification accounts.

Program Accomplishments--In fiscal year 1996, fifty-four master lots and 355 dosage form batches were certified.

Digoxin

Introduction--In 1974, digoxin certification procedures were established because of problems associated with oral digoxin products. The products were declared to be new drugs requiring ANDAs before marketing. Later the new drug declaration and ANDA requirements were stayed; however, the provision for batch certification remained to assure the uniformity of all marketed, unapproved, oral digoxin tablets.

Purpose--This program ensures that oral digoxin tablets meet the dissolution requirements under Title 21, Code of Federal Regulations, Section 310.500 and requirements of the United States Pharmacopeia.

Program Description--The division administers the Digoxin Certification Program that requires batch-by-batch certification. Samples of production lots submitted for certification are tested by the Center's Division of Drug Analysis. The results of this testing and the firm's CGMP status are considerations for certification. Based on recommendations by the analyzing laboratory and consultation with the jurisdictional district office, firms may be granted exemption from the certification process.

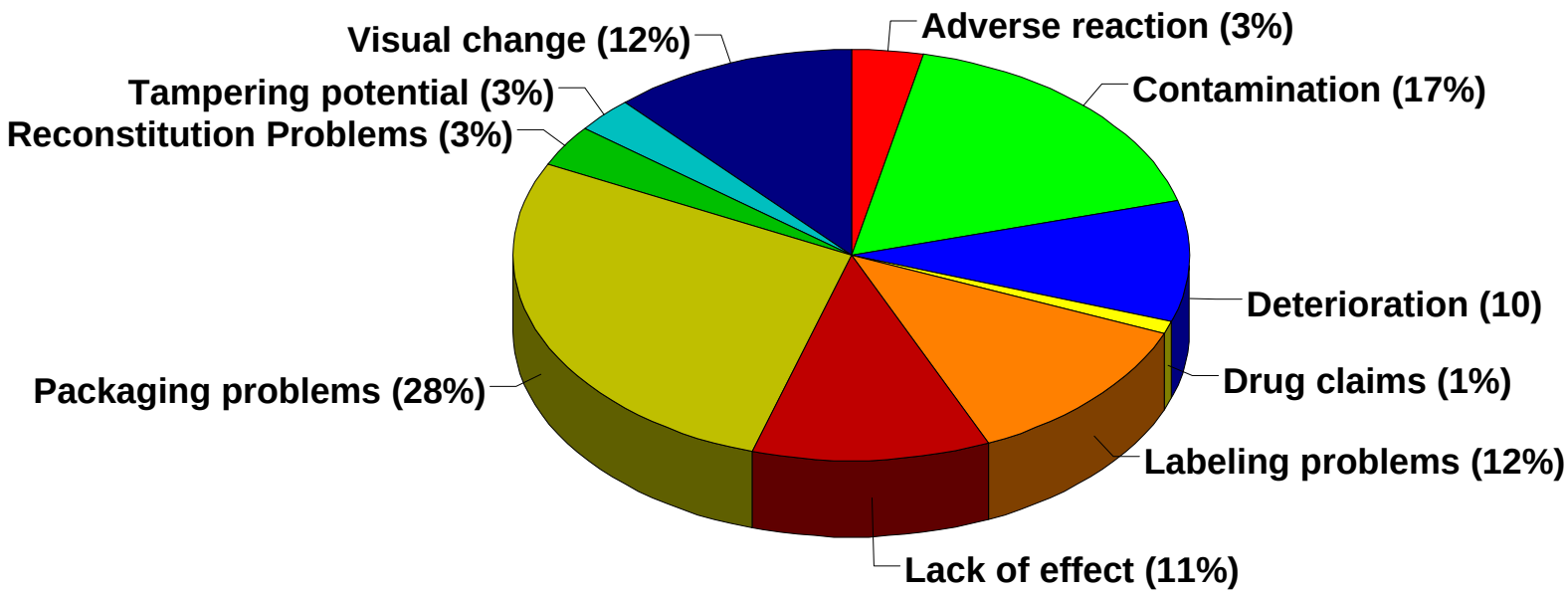
Program Accomplishments--During fiscal year 1996, nine lots of digoxin tablets were certified.

Compliance Activities--Two firms were granted exemption from the certification process.

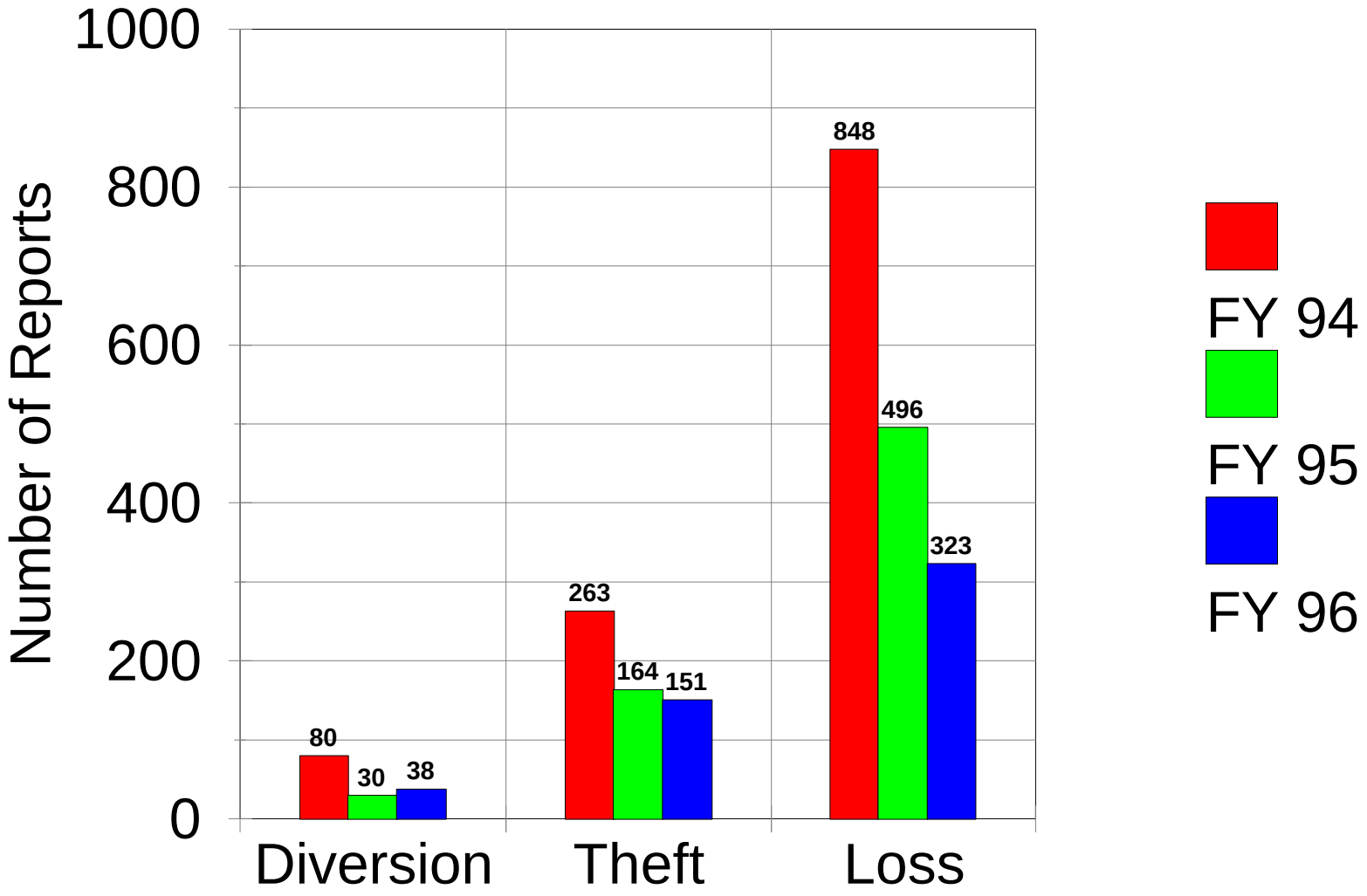
Drug Quality Reporting System

Primary Defects Reported

Fiscal Year 1996



Prescription Drug Marketing Act



SCIENTIFIC INVESTIGATIONS

David Lepay, MD, PhD
Director

Stan Woollen
Deputy

The Division of Scientific Investigations includes the Director's Staff, two Branches, (Clinical Investigations and Good Laboratory Practice and Bioequivalence Investigations), and two Teams, (Human Subject Protection and Narcotic Treatment Program). The division's functions protect human subjects, improve the quality of research, verify the data submitted in support of New Drug Applications and Abbreviated New Drug Applications, and assure compliance with Federal regulations. The principal program areas cover the regulation of:

- Clinical Trials
- *In Vivo* Bioequivalence Studies
- Nonclinical Laboratory Studies
- Institutional Review Boards
- Radioactive Drug Research Committees
- Narcotic Addiction Treatment Programs

Division of Scientific Investigations

David A. Lepay, MD, PhD
Director

Stan W. Woollen
Deputy Director

Clinical Investigations Branch Bette Barton, MD, PhD Branch Chief	GLP and Bioequivalence Investigations Branch C.T. Viswanathan, PhD Associate Director	Human Subject Protection Team Mary Jo Zollo Acting Team Leader	Narcotic Treatment Monitoring Program Team (Self-Directed)	Director's Staff
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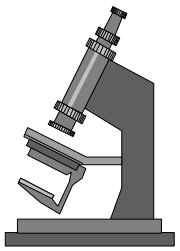
Robert SK Young, MD	Martin Yau, PhD			



DIVISION OF SCIENTIFIC INVESTIGATIONS

MISSION STATEMENT

We serve the American people by:

- Directing inspections of Institutional Review Boards and Radioactive Drug Research Committees for compliance with standards and regulations designed to protect the rights and welfare of human subjects participating in research
- Ensuring that investigators and sponsors who conduct pre-clinical and clinical studies on investigational new drugs comply with United States law and regulations covering good laboratory practices and good clinical practices
- Reviewing and verifying scientific data submitted to the FDA in support of applications to demonstrate the safety and efficacy of drugs for human use
- Inspecting and approving narcotic addiction treatment centers

BIORESEARCH MONITORING (BIMO) ACTIVITIES

Good Laboratory Practice (Non-Clinical Laboratories)

Introduction--Until the early 1970's, the FDA accepted most nonclinical laboratory study data submitted in support of marketing applications as resulting from appropriate experimental procedures conducted by a testing facility. The FDA would conduct for-cause inspections only in the most flagrant instances, for example, a review division is concerned about the consistency and validity of data, or studies of questionable purpose or design had been conducted, or a single research laboratory had simultaneously performed unusually large numbers of complex studies.

This changed when the FDA found significant deficiencies during inspections of testing facilities of major pharmaceutical firms and private contract laboratories that conducted studies on drugs and food additives. The agency was concerned that decisions about the safety of consumer products were being made based on data supplied by laboratories that lacked adequate standards and controls for what constituted good laboratory practice. As a result, during the mid-1970s Congress allocated additional funds specifically for assuring the quality and integrity of data submitted to the agency.

A Bioresearch Monitoring Program was established to address the issues related to preclinical testing and clinical research conducted in support of applications for products regulated by the FDA. Proposed regulations for Good Laboratory Practice (GLP) were published in 1976 and became final in December 1978. The GLP regulations apply to all nonclinical studies that support or are intended to support marketing applications for products regulated by the agency.

Purpose--Safety data from animal studies are needed to ensure that investigational drugs do not pose unnecessary risks to humans study subjects. The agency reviews and verifies the integrity and quality of the toxicology/pharmacology study data from both short- and long-term animal studies in Investigational New Drug (IND) Applications and New Drug Applications (NDAs). These data provide important information on the toxicity and possible adverse side effects of the study drug, and assist in the eventual identification of a safe dose to be used in human clinical studies.

Program Description--The division sets standards for the conduct of nonclinical laboratory investigations performed to prove the safety of human drugs, and designs and conducts surveillance and compliance programs for nonclinical drug product investigations. The division assigns, directs, and coordinates inspections of nonclinical drug product studies. In cooperation with CDER medical review divisions, the division

identifies and verifies critical toxicology and reproductive data in INDs and NDAs. The division also evaluates inspection reports for nonclinical laboratories, including commercial testing facilities (contract laboratories), for compliance with GLP regulations. The division evaluates inspectional data to provide an assessment of study quality to CDER review divisions and initiates necessary administrative and regulatory corrective measures.

Program Accomplishments--During fiscal year 1996, thirty-one inspections of non-clinical laboratories were conducted to determine compliance with GLP regulations (see charts pages 125 and 127). Thirty-eight assignments and inspection reports were received and Inspectional Observations were issued to fifteen facilities citing significant GLP violations. In addition, one comprehensive audit and GLP inspection revealed deviations so significant that the subject studies were considered not acceptable in support of safety for the IND under which they were submitted.

Compliance Activities-- In July 1996, the division audited three studies conducted by a major pharmaceutical company: a one-month rat pharmacokinetic study, a six-month rat pharmacokinetic study, and a chronic toxicity study in monkeys that was curtailed at five months when the animals became critically ill. The FDA's Division of Pulmonary Drug Products requested this audit based on conflicting conclusions from the two pharmacokinetic studies. (Note: These studies were performed to support an IND placed on clinical hold, i.e., the firm was not allowed to begin Phase 1 clinical studies [in human subjects] until notified by the FDA that it may proceed.)

The audit revealed problems with dosing in the rat studies. In addition, the audit found that the firm failed to perform appropriate serologic studies before starting the monkey study, and could not distinguish between effects caused by the monkeys' immuno-suppressive disease (simian retrovirus) and effects of the study drug. A list of GLP deficiencies was presented to the firm at the close of the inspection, and the inspection report recommended rejection of data from the monkey studies. The firm responded to the deficiencies and repeated a one-month rat pharmacokinetic study. However, the IND remains on clinical hold pending the outcome of additional studies.

Bioresearch Monitoring, Human Drugs-- *In Vivo* Bioequivalence

Introduction--Since the mid-1970s, the FDA has required NDAs and Abbreviated New Drug Applications (ANDAs) to contain evidence demonstrating bioavailability, i.e., evidence as to the rate and extent to which an active ingredient is absorbed and becomes available in the circulatory system. Two drugs may be considered bioequivalent if the rate and extent to which the active ingredient becomes bioavailable are not significantly different. The FDA's bioequivalence regulations were established to ensure that drug products intended to

be used interchangeably but have a known or potential bioequivalence problem are identified and adequately tested to assure they act in similar fashion. In this way, physicians can be assured a product selected for a patient will perform with reasonable consistency.

Purpose--The purpose of the *In Vivo* Bioequivalence Inspection Program is to audit data from bioequivalence studies under review at CDER. This will assure sound approval decisions and prompt follow-up action when gross problems occur, for example, fraud. Bioequivalence studies are generally performed to support a formulation change in an NDA or in support of an ANDA for a generic version of an innovator's drug product. The sponsor of an ANDA is required to show that an equivalent amount of an active ingredient in a generic drug product will achieve the same plasma drug concentration profile as produced by the innovator product.

Program Description--The division verifies the integrity of data from critical bioequivalence studies linking the formulation used during drug development (phase 2 and 3 studies performed to obtain clinical efficacy and safety information) with the current to-be-marketed formulation. In addition, the division evaluates the study conduct and data integrity supporting the first generic copy approved for each innovator drug product.

The division assists in investigating therapeutic failures of drugs and validates the data and the conduct of pivotal pharmacokinetic and pharmacodynamic studies submitted in support of new drug applications. The division evaluates inspection reports for commercial testing facilities and/or contract laboratories that conduct biopharmaceutic studies, and tracks “for cause” inspection requests from the review divisions and the Office of Generic Drugs (OGD).

Based on review of the inspection report and evaluation of study design, conduct, and data, the division may recommend that data be accepted or rejected. Rejection of data can block marketing of a product or require removal of an already marketed product.

Program Accomplishments--During fiscal year 1996, sixty-eight bioequivalence inspections were conducted (see charts pages 125 and 127) and fifty-one inspection reports were reviewed. Because of these reviews, the agency required five sponsors to conduct complete reanalyses of their data.

Compliance Activities-- Because of the division’s work, the agency changed the therapeutic equivalence code for propantheline bromide tablets (used to treat spasms of the gastrointestinal and urinary tracts) in the Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book). The FDA replaced the 'AA' (not having actual or potential bioequivalence problems) classification with a 'BP' (active

ingredients and dosage forms with potential bioequivalence problems) designation. The drug had been classified 'AA' under the Drug Efficacy Study Implementation (DESI) program from January 1977 until this reclassification in June 1996.

A well-controlled *in vivo* bioequivalence study submitted to OGD by the holder of the approved NDA for Pro-Banthine revealed that an approved generic version of the drug, which met the *in vitro* determination of bioequivalence, did not meet the agency's *in vivo* bioequivalence criteria. (To be considered bioequivalent, the peak concentration levels for the drug and the "area under the curve" must match the innovator's product within certain limits.) OGD examined the study and, in 1995, requested an inspection of the NDA holder's manufacturing facilities and the clinical study records of the contract laboratory. The audits conducted by the division verified the results of the study. The generic tablets did not perform within required limits.

Although the study proved neither bioequivalence nor bioinequivalence, it did raise significant concerns regarding the agency's original decision to classify the tablets as lacking actual or potential bioequivalence problems, and not to require an in vivo bioequivalence study to support the approval of generic versions. As a result, pending and new ANDAs for this drug require performance of an *in vivo* bioequivalence study rather than *in vitro* studies alone.

At the request of the Division of Anti-Infective Drug Products, the division audited both the analytical and clinical portions of two bioequivalency studies performed by a contract research organization on a drug to treat trichomoniasis. The purpose of the studies was to determine if a modified release tablet form of the drug (administered once a day) was bioequivalent to the same quantity of active drug administered in immediate release tablets (administered three times a day at evenly spaced intervals).

The FDA’s inspection of the clinical portion of the study revealed that the firm did not have a written policy for identifying statistical outliers (i.e., study subjects whose data fall outside acceptable limits of variation) and for excluding such data. Nevertheless, the firm identified one subject as an outlier because his area under the curve (AUC) value, the amount of drug that was bioavailable to this subject, was three times lower than the mean AUC value for all subjects. The firm applied a statistical test to decide that this subject was an outlier, but did not review the subject's clinical data or document any events that would suggest possible clinical reasons to support the outlier status. FDA investigators found nothing in this study subject's file--no use of concomitant medication or adverse effects--that could explain the stark difference in values and justify the firm's decision that this subject was an outlier. When the data for this subject were included in the firm's analysis, the oral modified release capsules were not bioequivalent to the immediate release tablets. If the data were excluded, the

two dosage forms were bioequivalent.

The agency found that the firm lacked standard operating procedures for conducting quality assurance checks of pharmacokinetic calculations. The firm developed computer software for its pharmacokinetic calculations and statistical outliers. However, the firm did not subject this software to any validation process and did not have a document describing the specifications, development, maintenance, upgrades, and security for this software.

Concurrent with its clinical inspection, the division began an investigation of the analytical portion of the study and several deviations from good laboratory practice were found. Plasma samples collected during the clinical studies were analyzed to detect and measure the quantity of the drug in the study subjects' plasma. At the time the analytical studies were done, the firm prepared calibration and quality control specimens from the same stock that was frozen and used throughout the study, but did so three to four months after receipt of the samples. The firm not only failed to evaluate the in-process stability of the drug, but lacked standard operating procedures to do so, and furthermore, failed to evaluate the extraction recovery for internal standards. Based on the findings, the Division of Anti-Infective Drug Products determined that the two dosage forms were not bioequivalent. The firm has responded to the agency's observations and has taken steps to correct deviations.

Clinical Investigator and Sponsor-Monitor Inspections

Introduction--In 1972, the FDA contracted with the National Academy of Sciences/National Research Council (NAS/NRC) to study issues in the monitoring of clinical investigations. NAS/NRC issued its findings to the agency in January 1973. In 1972, the FDA initiated a survey to determine current practices and procedures of both sponsors and investigators and determine what, if any, additional measures were needed to assure protection of human subjects in clinical trials. While the survey showed that grossly violative practices were infrequent, the survey did cite inattention to details important to high quality research, including frequent deficiencies in patient consent, protocol adherence, records availability, and records accuracy.

In July 1976, the General Accounting Office issued a report, "Federal Control of New Drug Testing is Not Adequately Protecting Human Test Subjects and the Public." At the same time, the FDA drafted regulations to implement the newly enacted Medical Device Amendments of 1976. These events and the FDA's concerns about the validity and integrity of data submitted from non-clinical studies prompted the agency to bring its case to Congress. They agreed that the agency needed to take action and allocated $16 million in additional funds to assure data quality and integrity. In 1977, the FDA

established a Bioresearch Monitoring Program to develop an agency-wide program to monitor preclinical testing and clinical research conducted in support of applications.

Purpose--Data audits are conducted on clinical investigations of human drugs to ensure that the research data are valid, scientifically sound, and accurate. and that investigators have adequately protected research subjects. Studies selected for an audit generally represent those for which safety and efficacy data have been determined as pivotal (most important) to support the decision to approve a new drug for marketing. Inspections are also conducted in situations of possible scientific misconduct, suspicion of fraudulent data, or potential lack of human subject protection by clinical investigators.

Program Description--The division designs and operates a monitoring program for clinical studies of investigational drugs. In cooperation with CDER's medical review divisions, the division selects for inspection those clinical studies that provide the safety and/or efficacy data that are pivotal to the agency's evaluation of NDAs. The division also assigns, directs, coordinates, participates in, evaluates, and classifies the inspections of clinical investigators, sponsors, monitors, and contract research organizations.

The division informs clinical investigators in writing of any recommended changes in their conduct of clinical trials. When serious noncompliance with FDA requirements is documented, the division initiates the appropriate administrative and/or criminal action against the responsible clinical investigator. The division provides guidance and instruction in good clinical practice to foreign and domestic clinical investigators, the pharmaceutical industry, and regulatory authorities.

Inspections are conducted when the agency is concerned about possible scientific misconduct, suspicious or fraudulent data, or the lack of adequate protection of human subjects of clinical studies. When study data are suspect, the division recommends that the data not be used in the evaluation of a new drug. These recommendations represent internal agency actions and cannot be made public due to the requirements of the Act.

Program Accomplishments--In fiscal year 1996, 404 inspections of domestic and foreign clinical investigators and nine inspections of sponsor-monitors and contract research organizations were completed (see charts pages 125 and 127). Most of these inspections were conducted to verify research data on human subjects, to determine that research was conducted in compliance with regulations, and to assure adequate protection of the rights and welfare of the human subjects.

The division classified 462 establishment inspection reports during fiscal year 1996. Of

these, 277 inspections were in violation of good clinical practice regulations. The division issued warning letters to nine clinical investigators. In addition, two clinical investigators signed consent agreements with the agency.

INTERNATIONAL CONFERENCE ON HARMONIZATION

The division participated actively for more than four years in the international effort to harmonize the good clinical practices of the European Union, Japan, and the United States. These efforts produced three guidelines: Guideline for Good Clinical Practice, Guideline for the Investigator's Brochure, and Guideline for Essential Documents for the Conduct of a Clinical Study.

The guidelines were prepared under the auspices of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. In 1996, the three ICH guidelines were combined into one guideline that is now known as the Good Clinical Practice: Consolidated Guideline. It was submitted to the regulatory authorities of the EU, Japan, and the US for implementation. After it publishes in the *Federal Register*, it will become a guideline in the US for good clinical practices and harmonizing standards for clinical trials involving human subjects.

INSTITUTIONAL REVIEW BOARDS (IRB) AND RADIOACTIVE DRUG RESEARCH COMMITTEES

Introduction--The first Federal requirement for Institutional Review Board (IRB) review occurred in 1953, when the Clinical Center at the National Institutes of Health (NIH) began certain review requirements for research conducted on hospitalized persons. These requirements include the review of nonstandard, potentially hazardous procedures to be performed on patients with the disease or condition being studied, and the review of procedures to be performed on normal subjects.

The first Federal requirements for informed consent were contained in the 1962 Kefauver-Harris amendments to the Food, Drug and Cosmetic Act, and the agency's 1963 IND regulations. Both provided for exceptions when consent was deemed not feasible or contrary to the subject's best interests.

In 1966, NIH began requiring IRB review for all NIH grant-supported extramural research to ensure that community standards would be considered in determining the acceptability of a proposed study. IRBs can make a better informed judgment about the risks and benefits of a proposed study than an individual subject--giving study subjects an additional level of protection. IRB review also supplements the use of informed consent as a safeguard of the rights and safety of study subjects. In June

1967, an FDA policy statement outlined for the first time what constituted consent and how it should be obtained. This policy specified that consent should be obtained in writing for phase 1 and phase 2 studies, but continued to allow oral consent in phase 3, if accompanied by a notation in the clinical record.

The first FDA regulations to require IRB review became effective in March 1971. IRB review was required only for study subjects who were institutionalized, e.g., in hospitals, nursing homes, and prisons. Studies to be conducted on outpatients were not included. The requirements for IRB review and informed consent were extended to all regulated clinical studies in 1981.

The benefits of institutional review are as follow:

- Appraisals of local conditions and standards,
- Sensitivity to the ethical and scientific concerns in the community and society,
- Acquaintance with investigators, subject groups and the setting in which the investigation is proposed to be conducted,
- Review of ongoing investigations and monitoring the safety of subjects,
- Adherence of the investigation to the approved protocol, other agreements, and applicable regulations, and
- Independence from competing interests.

Purpose--The division evaluates the actions of IRBs and Radioactive Drug Research Committees (RDRCs) as part of the Center's Bioresearch Monitoring Program. The division determines if IRBs and RDRCs are properly overseeing research by ensuring that the rights of participating human subjects are protected, and that the risks to human subjects are minimized.

Program Description--In cooperation with the Bioresearch Monitoring Programs of other Centers, the division sets standards of conduct for IRBs established to protect the rights and welfare of human research subjects. The division also sets similar standards for RDRCs that oversee studies involving radiopharmaceutical drug products. The division assigns, directs, and coordinates inspections of IRBs and RDRCs and evaluates compliance with Federal regulations. The division ensures that IRBs and RDRCs that do not comply with human subject protection requirements take corrective action, and monitors follow-up inspections or initiates administration action, if

appropriate. The division gives guidance to IRBs, RDRCs, clinical investigators, sponsors and consumers on Federal regulations. In addition, the division advises the Center's review divisions on the content of informed consent documents.

Program Accomplishments--During fiscal year 1996, 151 IRB and four RDRC inspections were conducted (see chart page 125). After the reports are reviewed, the agency's findings are expressed in letters. For serious deviations the IRBs are advised to make necessary corrections and to inform the agency of their actions. The FDA found 133 instances in which IRBs failed to comply with regulations to protect human subjects. Warning letters issued to five IRBs and one RDRC. Two IRBs signed consent agreements with the agency.

Under the Reinventing Government initiative and in cooperation with other Center units, the division redrafted the regulations for RDRCs to clarify the regulatory guidance and update the regulations to reflect new technologies, such as positron emission tomography (PET) scanners.

Compliance Activities--Inspection of the Ethical Board of Review (EBR), Inc., Austin, TX, revealed that although the EBR ceased operating in January 1994, the EBR failed to notify the FDA or clinical investigators. In addition, the IRB's Chair continued to issue letters to clinical investigators on the IRB's letterhead, falsely stating that continuing review of ongoing studies of investigational drug products had been accomplished at convened meetings. Inspection of the Charter Behavioral Health System of New Jersey, Summit, NJ, revealed that the IRB had not corrected any of the violations cited in a previous inspection conducted in 1990. Warning letters issued to both IRBs, and their owners signed consent agreements in which they agreed to cease operations and comply with all closure requirements.

In July 1996, Charles R. Pixley, President of Writers & Research, Inc., Rochester, New York, was sentenced by the U.S. Court for the Western District of New York to a year and a day in prison, probation for three years, 200 hours of community service, and a $500 fine. His conviction included one felony count of conspiring to defraud the FDA and 18 counts of introducing an unapproved drug into interstate commerce. The firm was separately found guilty on one felony count of conspiracy. The sentences brought a successful conclusion to a lengthy investigation involving the Division of Scientific Investigations, the Division of Labeling and Nonprescription Drug Compliance, and two agency field offices. Pixley's imprisonment has been postponed pending an appeal.

TASK GROUP ON INCLUSION OF WOMEN IN CLINICAL TRIALS

Representatives from the division and the Offices of Health Affairs, Women's Health, and AIDS and Special Health Issues formed a working group to explore concerns of obstacles to participation of women in clinical trials. The specific concern was that IRBs fail to carry out agency guidelines for inclusion of women in clinical trials and may impede women's participation by adding restrictions to study protocols. The working group developed a questionnaire requesting information about IRBs' policies and practices for inclusion of women in clinical studies for AIDS drugs. The questionnaire was distributed to 220 IRBs identified as having reviewed a study protocol for an AIDS drug within the previous two years. Seventy-one IRBs responded.

The working group uncovered no evidence of routine practices that might impede women's participation in clinical trials. Women were excluded from the AIDS trials in only two instances, however, in both instances the exclusion was justified. The IRBs approved both studies without requiring the inclusion of women. Overall, IRBs did have policies in place to include women in trials. However, IRBs that strove to include women in studies by rejecting studies that exclude women may have suffered negative consequences (loss of funding, research projects going to institutions having IRBs with less-stringent standards for review of study protocols, etc.).

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES LIAISON

During 1996, Marian Linde, R.N., Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), consulted weekly with the division regarding agency requirements for IRB review and informed consent. Her division is directly involved in research studies, and the experience increased NIAID's awareness of IRB authority and the responsibilities of clinical investigators and sponsors. Ms. Linde also shared the concerns and policy of the Division of AIDS, and mutual discussion of common problems regarding IRB review and informed consent benefitted both FDA and NIAID.

NARCOTIC TREATMENT PROGRAMS

Introduction--After enactment of the Comprehensive Drug Abuse Prevention & Control Act of 1970, FDA, the National Institute on Drug Abuse (NIDA), and the Drug Enforcement Administration (DEA) issued joint regulations covering the dispensing of methadone. Then, methadone was an

investigational drug used for the maintenance treatment of narcotic addiction. As illegal diversion of methadone became a serious problem in the early 1970's, Congress enacted the Narcotic Addict Treatment Act (NATA) of 1974. The NATA granted the Department of Health and Human Services authority to establish medical standards for practitioners who use narcotic drugs for either maintenance or detoxification treatment of narcotic addicts, and allowed methadone to be dispensed only by practitioners registered with DEA.

Until methadone was approved in December 1992 as a safe and effective drug for the maintenance treatment of narcotic addiction, it was subject to a restricted distribution system that was a hybrid between an investigational new drug and an approved new drug. Methadone remained the only approved drug available for that purpose until levo-alpha-acetyl-methadol (LAAM) was approved in July 1993.

The regulations have been updated periodically to clarify the conditions under which narcotic drugs may be dispensed, and to identify medical, counseling, rehabilitative and other social services that treatment centers were required or recommended to provide to addicts.

Purpose--The purpose of the Narcotic Treatment Program is to assure quality treatment of addicts and reduce the risk of diversion of narcotic drugs used for addiction treatment. The treatment of drug addicts with dependency-reducing drugs may reduce illicit drug use and the spread of AIDS, which is prevalent among IV drug users.

Program Description--The division sets standards for narcotic treatment programs; assigns, directs, and coordinates inspections of narcotic treatment centers; reviews inspection reports; and initiates corrective measures, as required.

The division ensures that care provided to patients in methadone treatment programs meets the standards established by Federal law. During emergencies the division assists State authorities in obtaining uninterrupted care for patients needing methadone treatment. To prevent diversion, the division in cooperation with DEA and State authorities evaluates and approves applications from narcotic treatment programs (outpatient treatment) and hospitals (inpatient treatment) for use of methadone and LAAM. Only those programs that comply with the narcotic treatment standards published jointly by the FDA and NIDA are approved.

The division trains and advises field investigators to conduct narcotic treatment program center inspections. Inspection reports are reviewed and evaluated for compliance with Federal regulations, exemptions are issued when appropriate, and

information about Federal regulations are given to State authorities and managers of narcotic treatment programs. Approximately 1,500 copies of the Narcotic Treatment Program Directory are prepared and distributed annually to treatment centers, and Federal, State and local authorities.

Program Accomplishments--Sixty-nine inspections of narcotic treatment programs were conducted, 3,414 program exception requests were reviewed, and seventy-six treatment applications and 271 program updates were reviewed and processed. Ten warning letters were issued and the agency proposed to revoke approval of one treatment program for violating Federal regulatory requirements. See chart page 129 for number of approved narcotic treatment programs.

Compliance Activities--In 1994, following a two-year study of the regulation of narcotic treatment programs, the Institute of Medicine recommended that a drug abuse treatment-oriented Public Health Service agency, such as the Substance Abuse and Mental Health Services Administration (SAMHSA), assume oversight of narcotic treatment programs. To ease the transfer of functions from the FDA to SAMHSA, staff from the division and other FDA units met with SAMHSA to discuss regulatory requirements for narcotic treatment facilities.

In May 1996, the division and the agency's Arlington Resident Post arranged a tour of Oasis, a narcotic treatment center in Washington, D.C. The purpose of the tour was to provide SAMHSA representatives with a firsthand look at a narcotic treatment program center and to give them a better understanding of the FDA's inspection process.

In 1995, a California narcotic treatment program entered a precedent setting consent agreement with the FDA. The consent agreement was negotiated after FDA inspections found eight of the treatment program's twenty-two methadone clinics to be in serious violation of the law and jeopardizing the safety and health of the patients. Terms of the agreement allowed the program to make corrections without interrupting the detoxification and maintenance services provided for patients.

During fiscal year 1996, the program secured the services of outside consultants to certify that its clinics comply with all Federal, State, and local laws for narcotic treatment programs, and established quality assurance and training programs for the clinics' staff. The program also established a $100,000 escrow account to pay for the cost of follow-up inspections by the FDA. The program sponsor met with the agency to report on the program's progress. Follow-up inspections of three approved narcotic treatment programs by outside experts revealed some minor deficiencies, which the program sponsor has promised to correct. The FDA inspections will commence following evaluation of the experts' report.

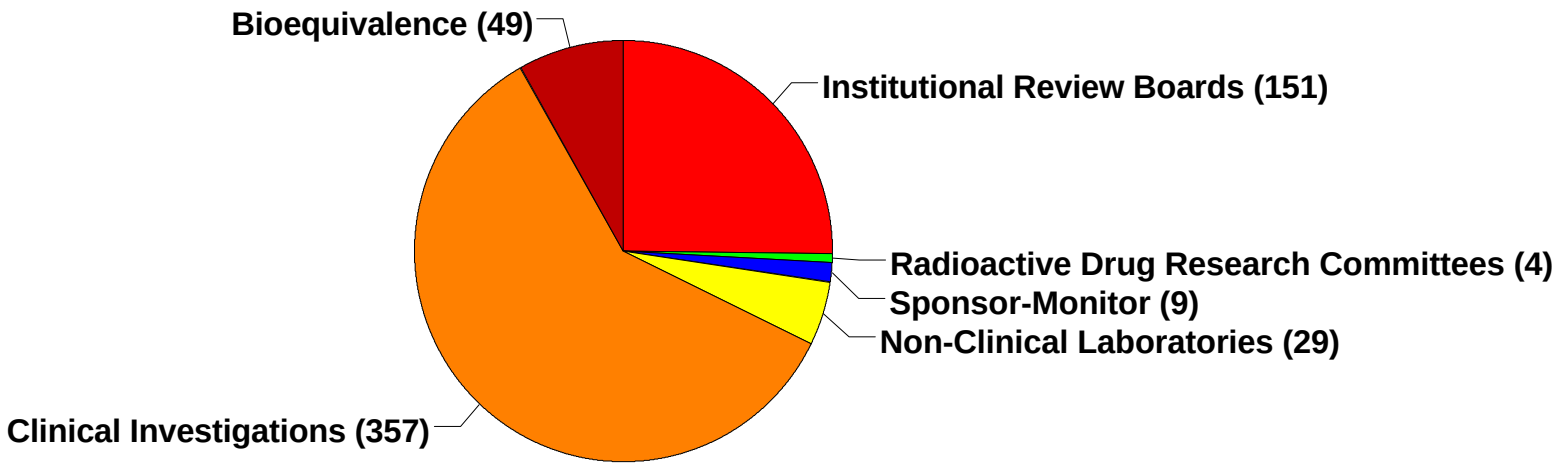
Foreign BIMO Inspections

Fiscal Year 1996

Countries Visited	Number of Inspections
Australia	3
Belgium	6
Brazil*	3
Canada	16
Costa Rica*	1
Denmark	1
Finland	4
France	6
Germany	5
Israel	1
Italy	2
Netherlands	3
Peru*	1
Russia*	2
Scotland	1
Slovenia*	2
Spain	2
Sweden	3
United Kingdom	6

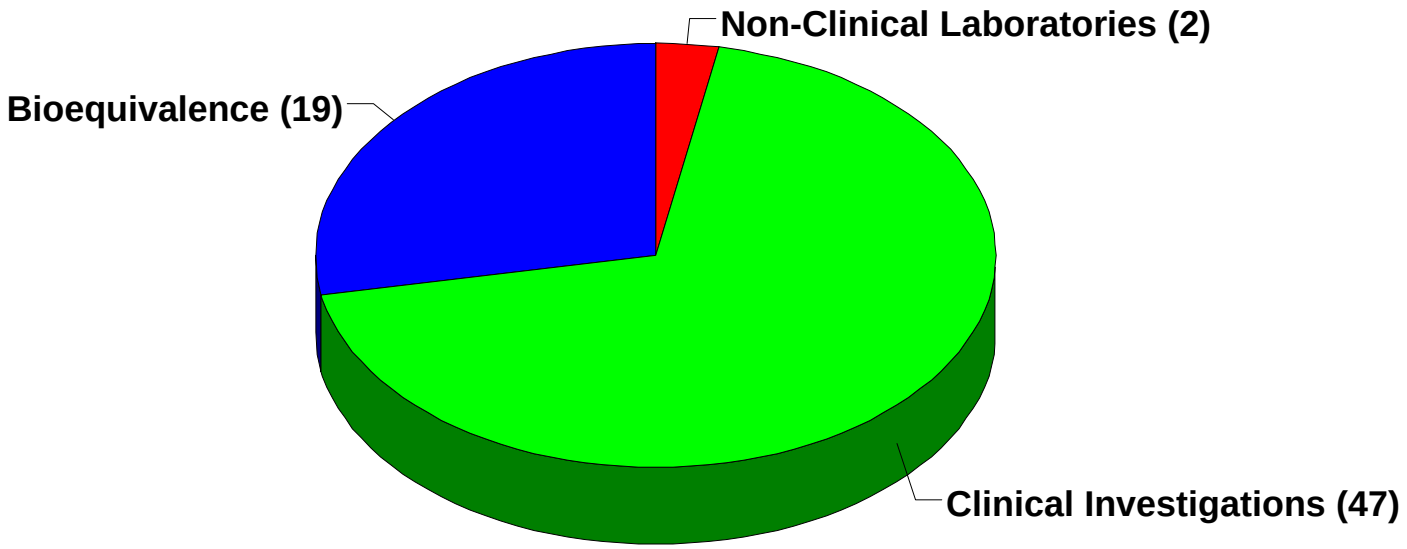
Total: 68 Inspections
*Country not previously visited

Bioresearch Monitoring Inspections
FY 96



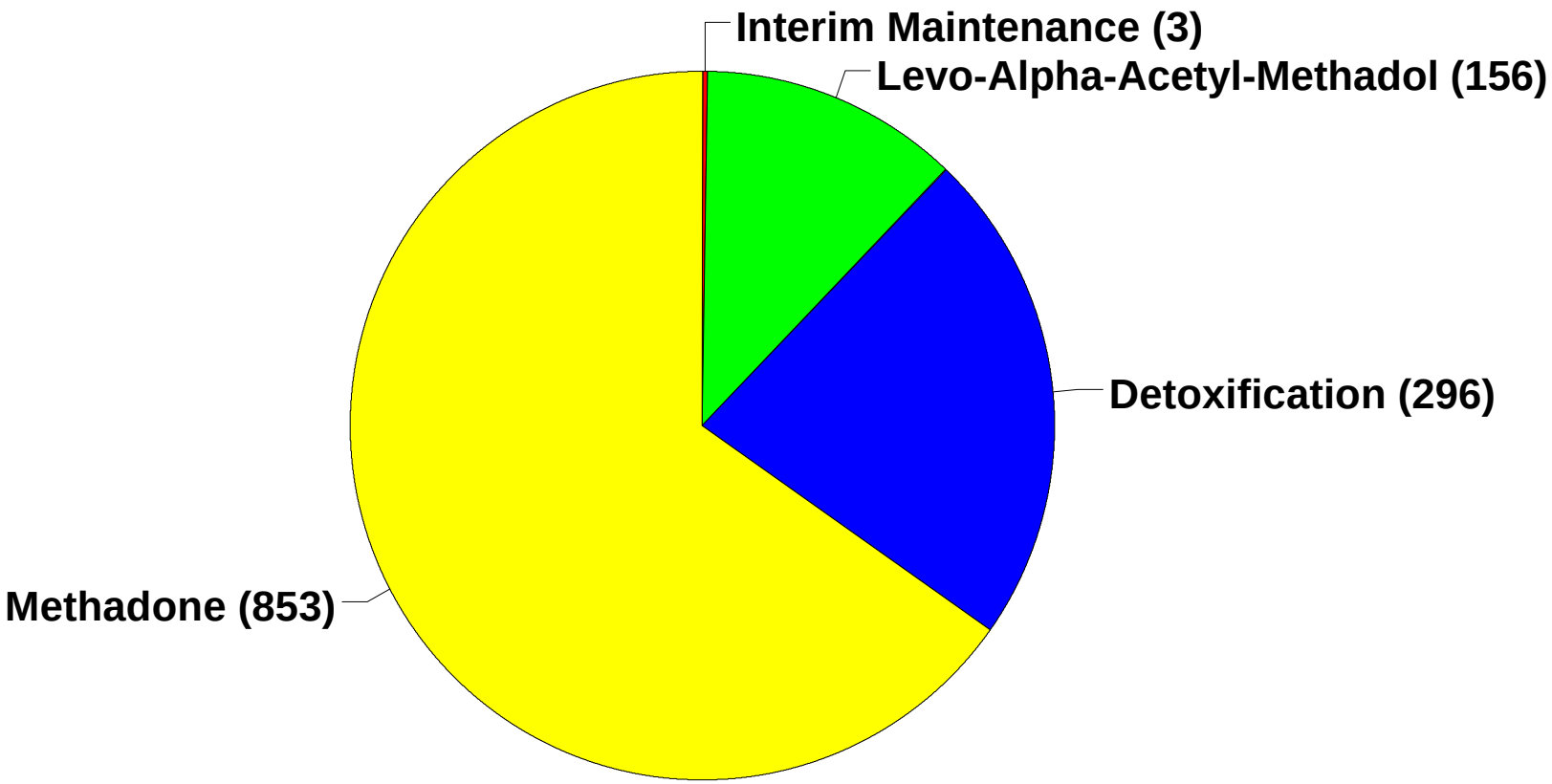
Bioresearch Monitoring Inspections

Foreign



Total Sites: 68

Approved Narcotic Treatment Programs



COMPLIANCE ACHIEVEMENTS

Definitions

CITATION

The section 305 Notice is a statutory requirement of the Federal Food, Drug, and Cosmetic Act. It provides the defendant with an opportunity to show cause why he should not be prosecuted for the alleged violation. Response to the notice may be by letter, personal appearance or no response.

INJUNCTION

An order issued by the Court requiring a defendant to do or refrain from doing a specified act.

PROSECUTION

A criminal action directed against a firm and/or responsible individuals. It is punitive with the view of punishing past behavior and obtaining future compliance.

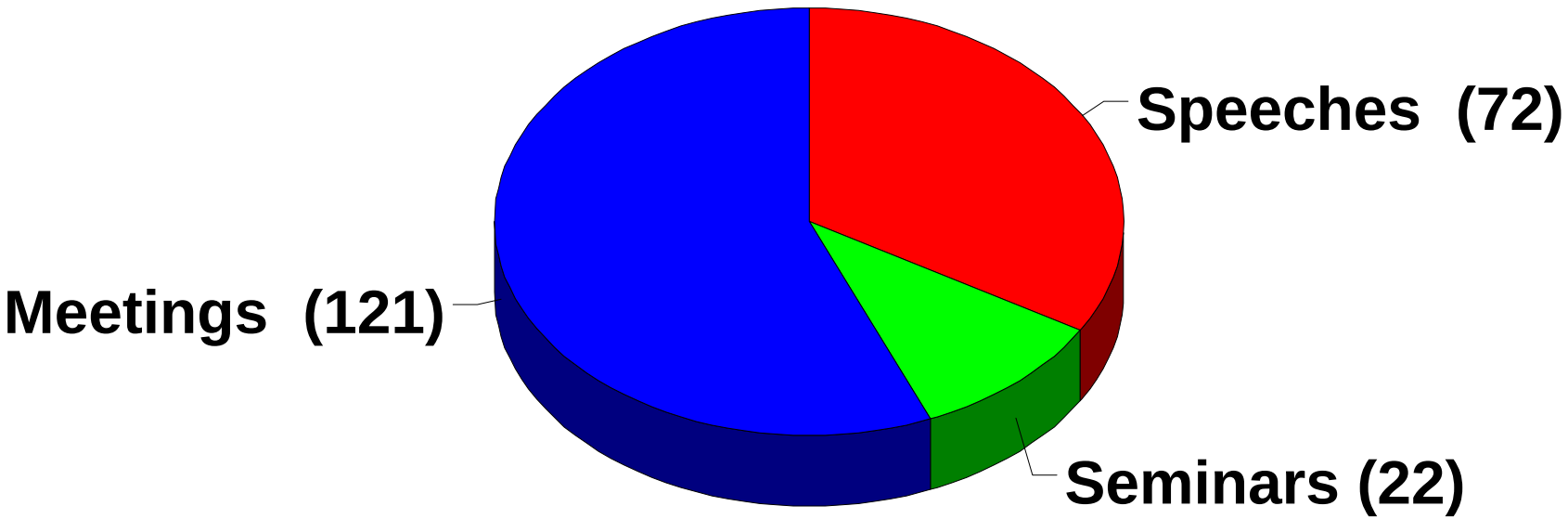
WARNING LETTER

A written communication from the FDA notifying and individual or firm that the agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act, or other acts, and that failure of the responsible party to take appropriate and prompt action to correct and prevent any future repeat of the violation may result in administrative and/or regulatory enforcement action without further notice.

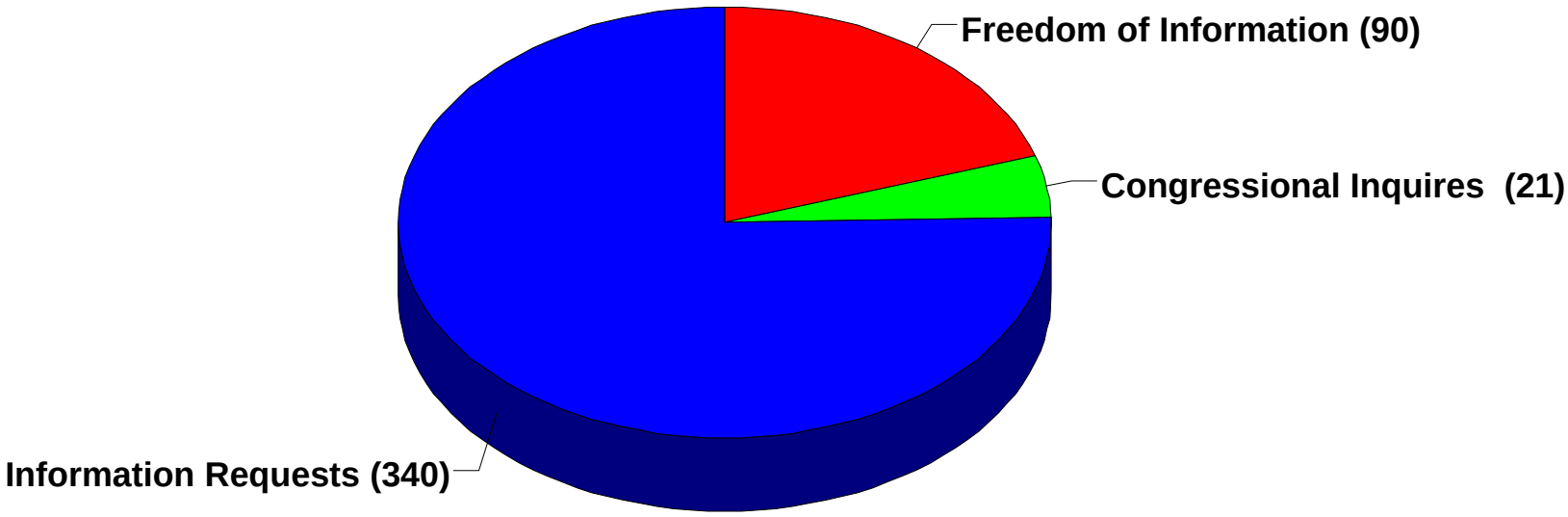
SEIZURE

Attachment of goods through Court order by a U.S. Marshal pursuant to Section 304 of the Federal Food, Drug, and Cosmetic Act.

Educational Activities With Industry

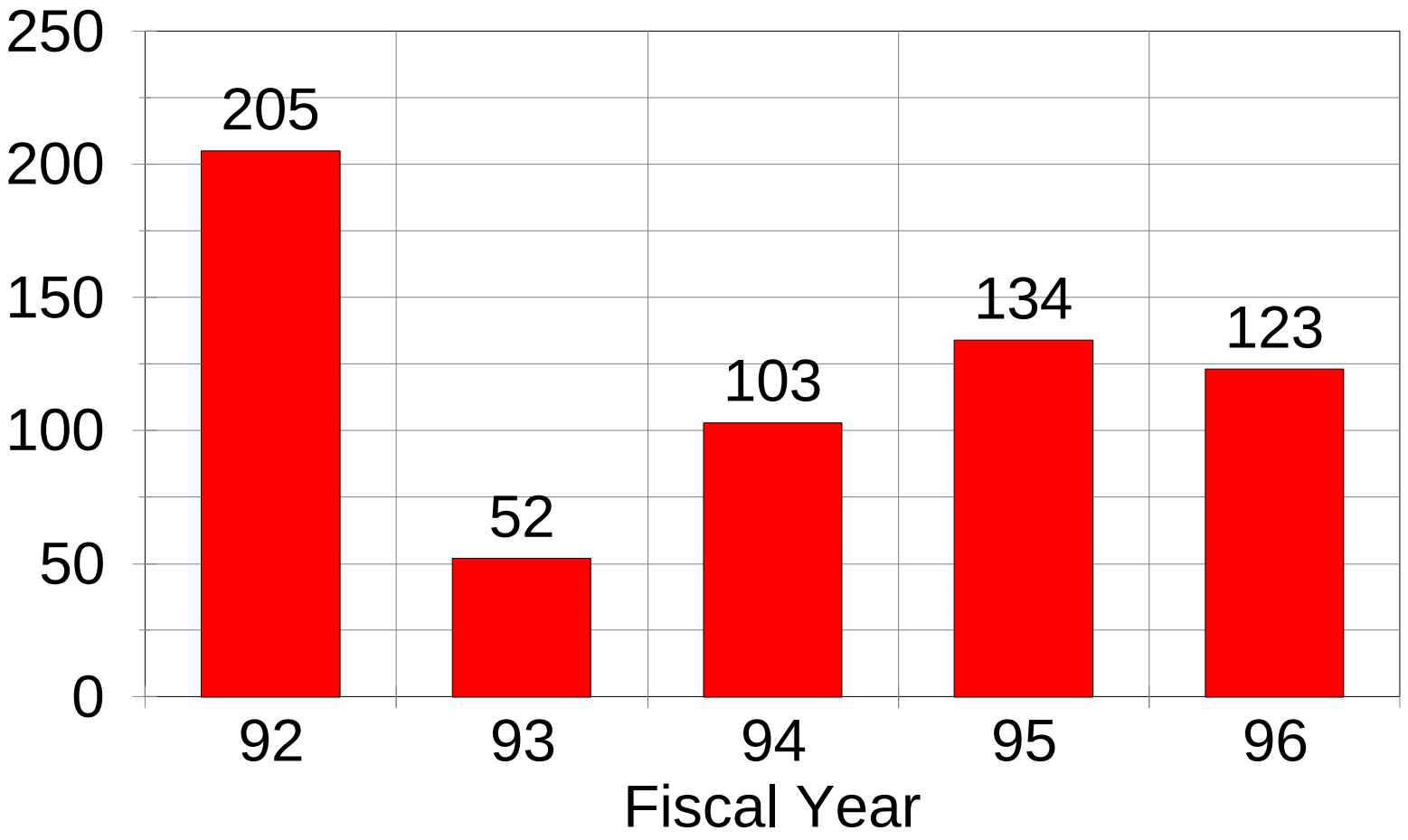


Controlled Correspondence



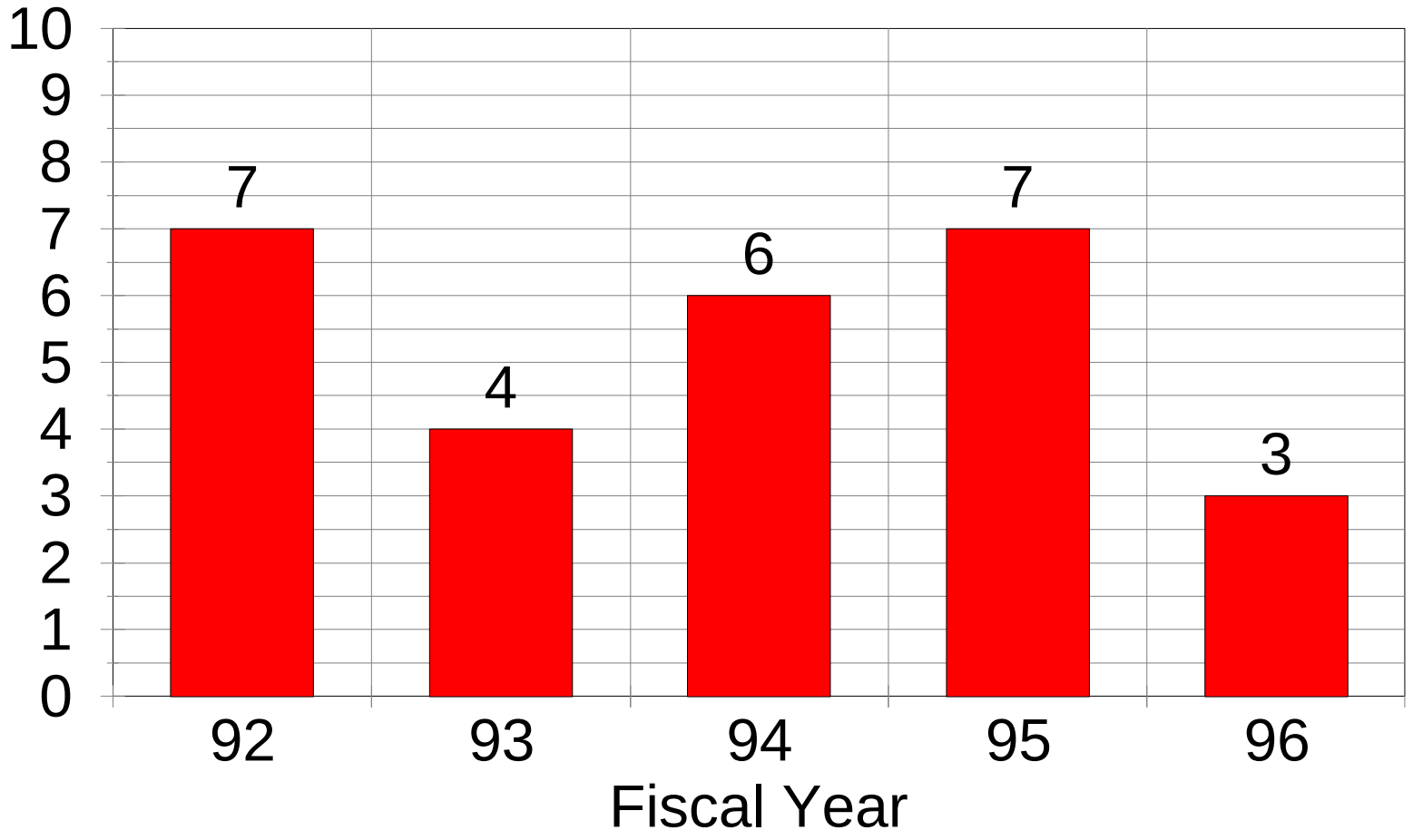
Warning Letters

Approved by Office of Compliance



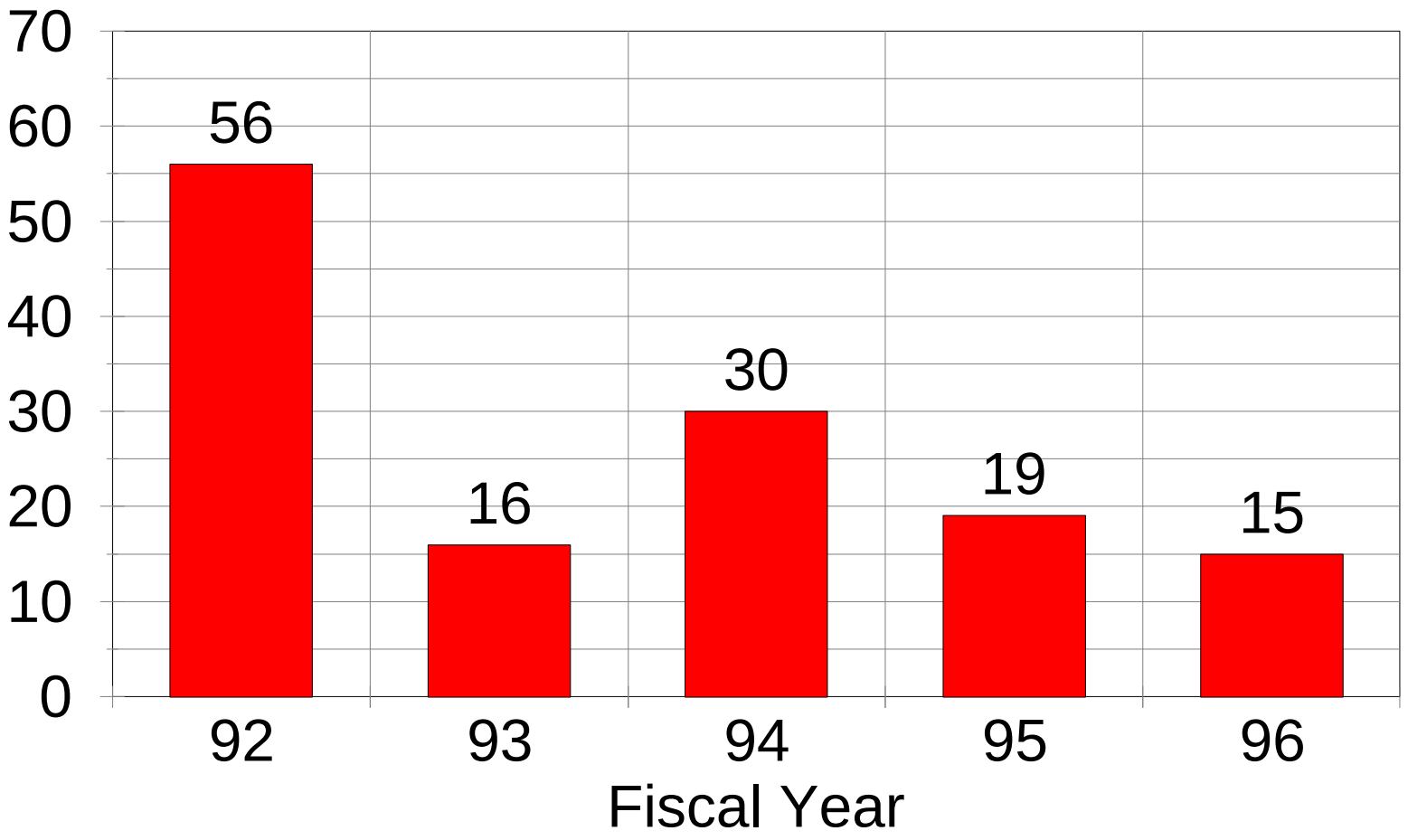
Injunctions

Approved by Office of Compliance



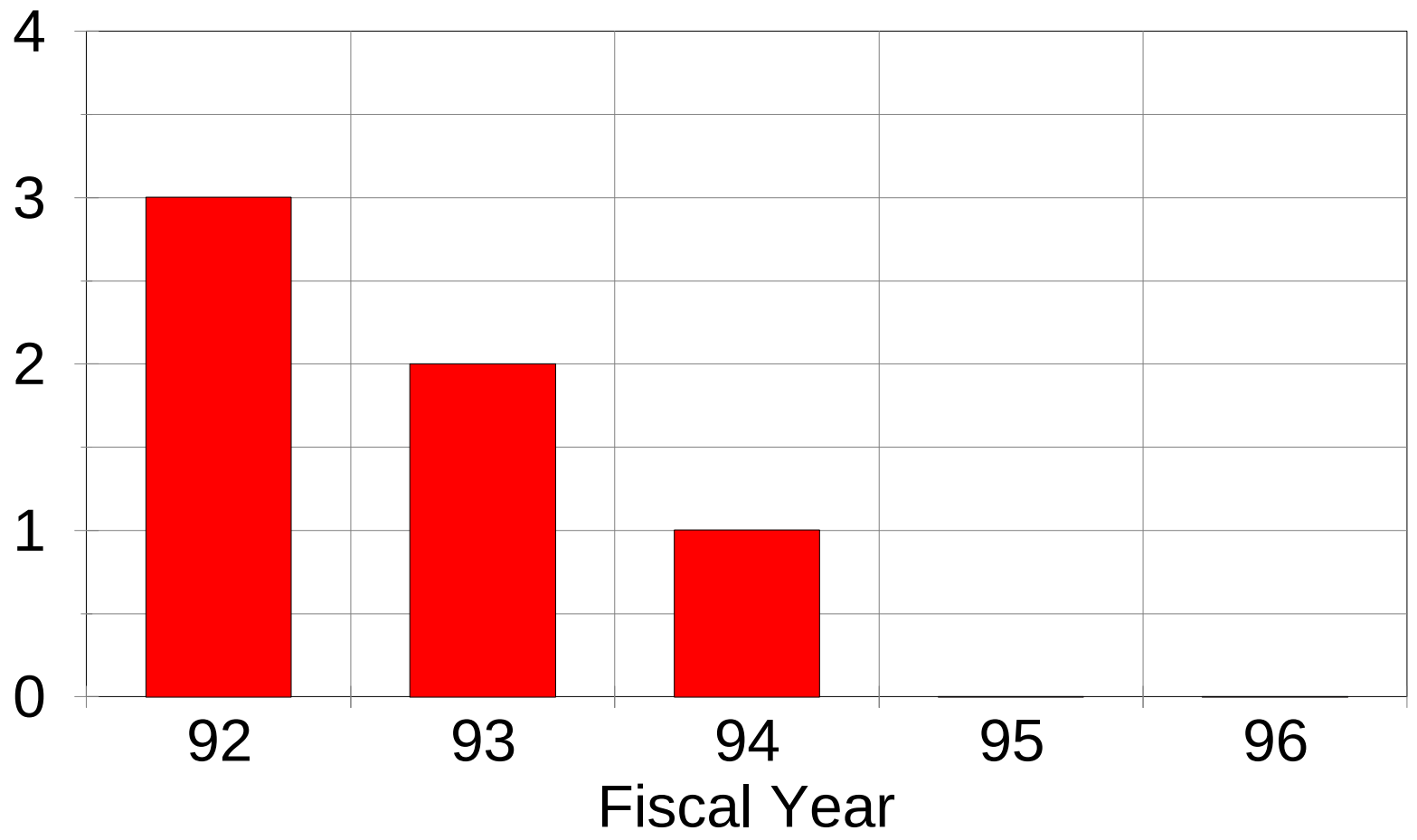
Seizures

Approved by Office of Compliance



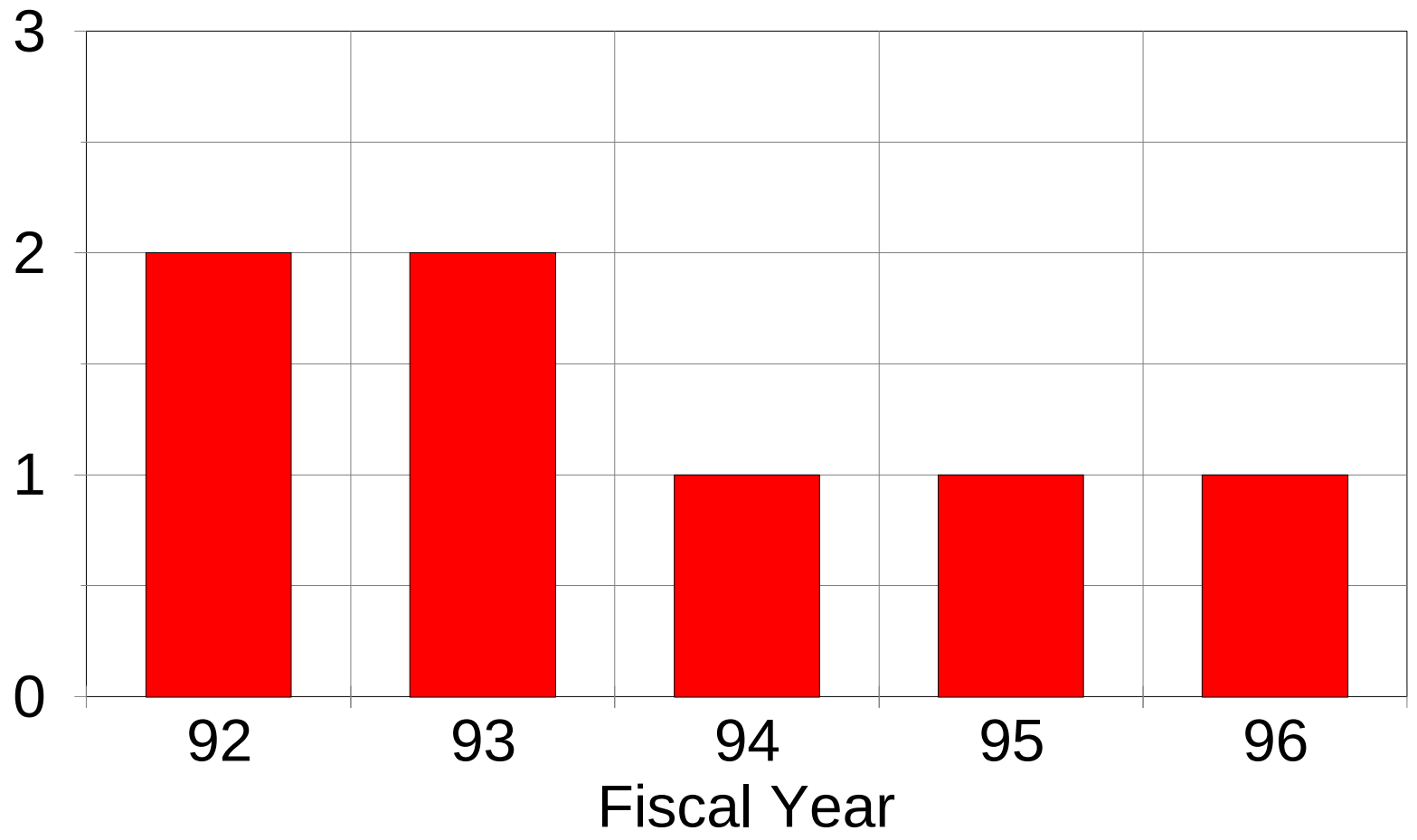
Citations

Approved by Office of Compliance



Prosecutions & Grand Jury

Approved by Office of Compliance



SPECIAL RECOGNITION

SPECIAL RECOGNITION

1996 Ronald H. Brown Award

Presented to the Center for Drug Evaluation and Research in recognition of technical assistance to Israel.

FDA Award of Merit

Douglas Ellsworth

FDA COMMISSIONER'S SPECIAL CITATION

Betty L. Jones

Hammer Award

Duane Sylvia

Public Health Service Unit Commendation Award

Matthew Tarosky, R.Ph.

FDA Biotech Regulatory Workshop Group Recognition Award

Stephanie R. Gray

CDER Restructuring Team Group Recognition Award

Anita Harrell

Recognition Awards

Kathy Anderson
Joel A. Aronson
Willie C. Becoat (New York District)
Pat Beers Block
Tawni Brice (2)

Kevin Budich
Constance Bulawka
Flora Chang
Roma Egli (2)
Robert Eshelman (2)
Roxana Fay
Shirnette Ferguson
Rick L. Friedman
Herb Gerstenzang
Candice Hamilton (3)
James Hamilton
Angela N. Harris (2)
Brian Hasselbalch
Carolyn Hommel
Lavonia Huff
Hea S. Kiel
Shirley Kline
Jonathon Lane

Marilyn Leach
Donald Leggett
Jacqueline S. Leung (2)
Jocelyn V. Lewis
Patricia Maroney (Mid-West Region)
Linda McGee
Betty McRoy
Edward Miracco (2)
Kathy Miracco
Peggy Noland (2)
Patricia Noyes
William Nychis
Margaret O'Rourke
George Prager
Lana Ragazinsky
Thomas Selnekovic
Vesna Stanoyevitch
Karen Storms (2)
Mary Thompson
Donald Wisner
Michael Verdi
Marilyn Wolf (3)
Mary Jo Zollo

Quick Reference List

QUICK REFERENCE LIST

Acne Products	Constance E. Bulawka HFD-312	301/594-1065
Active Pharmaceutical Ingredients		
	Edwin Rivera HFD-322	301/594-0095
Unapproved	Ada Irizarry HFD-300	301/594-0101
CDER Working Group	Paul Motise HFD-325	301/594-0098
(OC representatives)	Edwin Rivera HFD-322	301/594-0095
	Pat Beers Block HFD-320	301/594-0093
	Richard Lev HFD-325	301/594-0098
Acute Toxic Ingestion	Edward Miracco HFD-314	301/594-0070
ADP (Automated Data Processing)		
	Tom Selnekovic HFD-300	301/594-0054
Adverse Drug Experience Reporting		
	Nancy Haggard HFD-332	301/594-0101
	Denis Mackey HFD-332	301/594-0101
Alcohol Drug Products (Topical)		
	Kevin Budich HFD-312	301/594-1065
Anorectals (Hemorrhoidals)		
	Flora Chang HFD-312	301/594-1065
Antacids	Robert Eshelman HFD-312	301/594-1065
Anthelmintic	Edward Miracco HFD-314	301/594-0070
Anticaries	Robert Eshelman HFD-312	301/594-1065
Antiemetics	Jonathan Lane HFD-312	301/594-1065
Antiperspirants	Constance E. Bulawka HFD-312	301/594-1065
Aphrodisiacs	Edward Miracco HFD-314	301/594-0070

Application Integrity Policy (AIP)		
Data Integrity Inspections		
	Bruce Hartman HFD-324	301/827-0067
Implementation	LuAnn Pallas HFD-325	301/594-0098
Aseptic Processing	Richard Friedman HFD-322	301/594-0095
	Michael Verdi HFD-301	301/594-0054
	Tracy Roberts HFD-325	301/594-0098
Audio Visual Equipment	Administrative Staff * HFD-305	301/594-1058
Awards	Anita Harrell HFD-305	301/594-1058
Barrier Isolation Technology		
	Richard Friedman HFD-322	301/594-0095
	Michael Verdi HFD-301	301/594-0054
Basic Drug School	Paul Motise HFD-325	301/594-0098
Benign Prostatic Hypertrophy		
	Roma Egli HFD-314	301/594-0070
Bioequivalence (In Vivo)	C.T. Viswanathan, PhD HFD-345	301/594-1023
Biopharmaceutics	C.T. Viswanathan, PhD HFD-345	301/594-1023
Bioresearch Monitoring (BIMO)		
Program Manager	Stan W. Woollen HFD-341	301/594-0020
Regulatory Manager	George Prager HFD-344	301/594-1029
Data Managers:		
Clinical Data Analysis		
	Carolanne Currier HFD-344	301/594-1032
GLPs	Ty Fujiwara HFD-345	301/594-1023
Protection of Human Subjects		
	Nancy Pursell HFD-343	301/594-1026
PDUFA Issues	David A. Lepay, MD, PhD HFD-340	301/594-0020
Biotechnology	Brian Nadel HFD-325	301/594-0098
Boil Ointments	Flora Chang HFD-312	301/594-1065
Budget	Anita Harrell HFD-305	301/594-1058

Camphorated Oil	Roma Egli HFD-314	301/594-0070
Case Management		
BIMO Programs	Stan W. Woollen HFD-341	301/594-0020
	George Prager HFD-344	301/594-1029
New Drug Charges-OTC		
	Robert Eshelman HFD-312	301/594-1065
	A. Joel Aronson HFD-314	301/594-0070
New Drug Charges-Rx	Margaret O'Rourke HFD-330	301/594-0101
	Ada Irizarry HFD-330	301/594-0101
	Mel Szymanski HFD-332	301/594-0101
	Ray Fazzari HFD-330	301/594-0101
CGMP Drug Quality	Joseph Famulare HFD-320	301/594-0098
Pre- & Post-Approval	Mark Lynch HFD-324	301/827-0062
	Bruce Hartman HFD-324	301/827-0067
Sterilization	Richard Friedman HFD-322	301/594-0095
	Michael Verdi HFD-301	301/594-0054
	Tracy Roberts HFD-325	301/594-0098
Central Pharmacy Sterile Compounding Committee		
	LuAnn Pallas HFD-325	301/594-0098
Certificates to Foreign Governments		
	Import/Export Team HFD-316	301/594-3150
Certificates of Pharmaceutical Product		
	Import/Export Team HFD-316	301/594-3150
CGMP Guidelines	Paul Motise HFD-325	301/594-1089
CGMP for Pharmacies	LuAnn Pallas HFD-325	301/594-0098
CGMP Policy	Division of Manufacturing and Product Quality HFD-320	301/594-0098
CGMP Revision Committee (FDA)		
	John Dietrick HFD-322	301/594-0095
	Paul Motise HFD-325	301/594-0098
	Richard Lev HFD-325	301/594-0098
Cholecystokinetics	Robert Eshelman HFD-312	301/594-1065

Civil Litigation Guidance		
New Drug Charges-OTC		
	Robert Eshelman HFD-312	301/594-1065
	A. Joel Aronson HFD-314	301/594-1065
New Drug Charges-Rx	Ada Irizarry HFD-330	301/594-0101
	Mel Szymanski HFD-332	301/594-0101
	Ray Fazzari HFD-330	301/594-0101
CGMP	Nick Buhay HFD-325	301/594-0098
Clandestine Drug Distribution		
	Don Leggett HFD-316	301/594-3150
Clinical Studies	Bette Barton, MD, PhD HFD-344	301/594-1032
Clinical Supplies/IND CGMP		
	Paul Motise HFD-325	301/594-0098
	Bruce Hartman HFD-324	301/827-0067
CMCCC Compliance Representatives		
Analytical Methods	C.T. Viswanathan, PhD HFD-345	301/594-1023
	Monica Caphart HFD-325	301/594-0098
Biotechnology	Brian Nadel HFD-325	301/594-0098
Complexing Agents	Pat Alcock HFD-322	301/594-0095
Drug Master File	Richard Lev HFD-325	301/594-0098
Drug Product	LuAnn Pallas HFD-325	301/594-0098
Drug Substance	Edwin Rivera HFD-324	301/594-0095
Gelatin Capsules	Nick Buhay HFD-325	301/594-0098
Guidance Documents		
SUPAC MR	Pat Beers Block HFD-325	301/594-0093
SUPAC TDS	Brian Hasselbalch HFD-325	301/594-0098
BACPAC	Edwin Rivera HFD-322	301/594-0095
PASPAC	Michael Verdi HFD-301	301/594-0054
Labeling & Nomenclature		
	Puri Subramaniam HFD-333	301/594-0107
Liposomes	Pat Alcock HFD-322	301/594-0095
Packaging	Sonia Crisp HFD-333	301/594-0101
	Edwin Melendez HFD-325	301/594-0098
Photostability	Russ Rutledge HFD-325	301/594-0098
Stability	Barry Rothman HFD-325	301/594-0098
Tests & Specifications	Richard Friedman HFD-322	301/594-0095
Cold Sore/Fever Blister	Jonathan Lane HFD-312	301/594-1065

Colloidal Silver	Roma Egli HFD-314	301/594-0070
Communication Committees (OTCOM)		
	Betty Jones HFD-301	301/594-0054
	Randall Woods HFD-324	301/827-0062
Compliance Coordinating Committee		
Chair	Stephanie Gray HFD-300	301/594/0054
Executive Secretary	Pat Beers Block HFD-320	301/594-0093
Compliance Program Clearance		
	Andrea Schaub HFD-336	301/594-0107
Computer Applications	Tom Selnekovic HFD-300	301/594-0054
Computer Specialist	Tom Selnekovic HFD-300	301/594-0054
	Roxana Fay HFD-310	301/594-0063
Computer Validation		
CGMPs	Paul Motise HFD-325	301/594-0098
GLPs	Charles Snipes, PhD HFD-345	301/594-1023
Conference Room Scheduling (MPN 254 & 259)		
	Office of the Director HFD-300	301/594-0054
Content Uniformity Test	Monica Caphart HFD-325	301/594-0098
	Russ Rutledge HFD-325	301/594-0098
Contract Research Organizations		
	Carolanne Currier HFD-344	301/594-1032
Corn & Callous Removers	Constance E. Bulawka HFD-312	301/594-1065
Cosmeceuticals	Roma Egli HFD-314	301/594-0070
	Jan Davis - backup HFD-314	301/594-0070
Cough/Cold Products	Robert Eshelman HFD-312	301/594-1065
Counterfeit/Imitation	Don Leggett HFD-316	301/594-3150
Criminal Litigation Support		
CGMP	Nick Buhay HFD-325	301/594-0098
OTC Drug Issues	Bradford W. Williams HFD-310	301/594-0063
	Don Leggett HFD-316	301/594-3150

Rx Drug Issues	Ada Irizarry HFD-300	301/594-0101
	Mel Szymanski HFD-332	301/594-0101
PDMA	Margaret O'Rourke HFD-330	301/594-0101

Customer Service Task Force (FDA)

	Betty Jones HFD-301	301/594-0054

Dandruff/Seborrhea/Psoriasis

	Flora Chang HFD-312	301/594-1065

Dental Products (OTC)	Robert Eshelman HFD-312	301/594-1065
(Rx)	HFD-330	301/594-0101

DESI (Drug Efficacy Study Implementation)

	Herb Gerstenzang HFD-330	301/594-0101
	Ada Irizarry HFD-330	301/594-0101

Diaper Rash Products	Kevin Budich HFD-312	301/594-1065

Digestive Aids	William A. Russell HFD-314	301/594-0070

Digoxin Certification	Puri Subramaniam HFD-333	301/594-0107

Dissolution	Monica Caphart HFD-325	301/594-0098
	Russ Rutledge HFD-320	301/594-0093

Document Room Committee (OC)

	Anita Harrell HFD-305	301/594-1058
	Jackie Leung HFD-310	301/594-0063
	Jim Hamilton HFD-316	301/594-3150
	Dave Doleski HFD-324	301/827-0072
	Nick Buhay HFD-325	301/594-0098
	Carolanne Currier HFD-344	301/594-1032
	Bob Meyer HFD-343	301/594-1026

Drug/Cosmetic Labeling (Policy)

	A. Joel Aronson HFD-314	301/594-0070

Drug/Device Issues	Margaret O'Rourke HFD-330	301/594-0101
	Rita Hoffman HFD-332	301/594-2073

Drug/Dietary Supplement Health and Education Act (Policy)

	A. Joel Aronson HFD-314	301/594-0070

Drug Diversion		
OTC Sale of Legend Drug		
	Don Leggett HFD-316	301/594-3150
PDMA	Margaret O'Rourke HFD-330	301/594-0101
Drug/Food Labeling Issues		
	A. Joel Aronson HFD-314	301/594-0070
Drug/Nutrition Labeling and Education Act		
	A. Joel Aronson HFD-314	301/594-0070
Drug Product Code Work Group (CDER/DIOP)		
	Michael Verdi HFD-301	301/594-0054
Drug Product Surveillance Surveys		
	Andrea Schaub HFD-336	301/594-0107
	Jay Schmid	301/504-0107
Drug Quality Reporting System		
	Roger Gregorio HFD-336	301/594-0107
	Lana Ragazinsky HFD-336	301/594-0107
Drug Shortage Issues	Michael Verdi HFD-301	301/594-0054
Drug Stability	Barry Rothman HFD-325	301/594-0098
Eastern European MOU	Bradford W. Williams HFD-310	301/594-0063
Electronic Records/Signatures		
	Paul Motise HFD-325	301/594-1089
EPA Liaison	Robert Eshelman HFD-312	301/594-1065
EPMS	Anita Harrell HFD-305	301/594-1058
Equivalency Work Group	Brian Hasselbalch HFD-325	301/594-0098
	Pat Beers Block HFD-320	301/594-0093
Establishment Evaluation System (EES)		
Coordinators	Shirnette Ferguson HFD-324	301/827-0068
	Melissa Egas HFD-322	301/827-0095
Ombudsman	Bruce Hartman HFD-324	301/827-0067

European Union MOU	Stephanie Gray HFD-300	301/594/0054
	Pat Beers Block HFD-320	301/594-0093
	Brian Hasselbalch HFD-325	301/594-0098
	Pat Alcock HFD-322	301/594-0095
GLPs	Stan W. Woollen HFD-341	301/594-0200
Exocrine Pancreatic Insufficiency		
	Flora Chang HFD-312	301/594-1065
Export for Clinical Studies CFR 312.110		
	Jim Hamilton HFD-316	301/594-3150
Export of Unapproved New Drugs Under § 801 & 802 of FD&C ACT		
	Jim Hamilton HFD-316	301/594-3150
External Analgesics/Liniments		
	William Nychis HFD-312	301/594-1065
Facilities (Building complaints)		
	Administrative Staff * HFD-305	301/594-1058
Facility Reviews	Russ Rutledge HFD-320	301/594-0093
FACTS (Field Accomplishment and Compliance Tracking System)		
	Office of Compliance HFD-300	301/594-0054
	Tom Selnekovic HFD-301	301/594-0054
	Mark Lynch HFD-324	301/827-0062
	John Singer HFD-324	301/827-0071
	Richard Friedman HFD-324	301/594-0095
	Michael Verdi HFD-301	301/594-0054
	Kathy Miracco HFD-330	301/594-0101
FTC (Federal Trade Commission) Liaison		
	A. Joel Aronson HFD-314	301/594-0070
FTEs	Anita Harrell HFD-305	301/594-1058
Field Alert Report (NDA/ANDA)		
	Roger Gregorio HFD-336	301/594-0107
	Jay Schmid HFD-336	301/594-0107
Field Drug Committee Liaison		
	Pat Beers Block HFD-320	301/594-0093

FOI (GLP Foreign EIs)	Ty Fujiwara HFD-345	301/594-1023
(IRB/Informed Consent)		
	Nancy Pursell HFD-343	301/594-1026
(DQRS)	Roger Gregorio HFD-336	301/594-0107
Foreign Inspections		
BIMO	Stan W. Woollen HFD-341	301/594-0200
Foreign Inspection Team Leader		
	John Dietrick HFD-322	301/594-0095
Generic Drug Enforcement Act Work Group		
	Barry Rothman HFD-325	301/594-0098
GLP (Good Laboratory Practices)		
	C. T. Viswanathan, PhD HFD-345	301/594-1023
Government-Wide Quality Assurance Program (GWQAP)		
	Joseph Famulare HFD-325	301/594-0098
GPRA (Government Performance and Results Act)		
	Betty Jones HFD-300	301/594-0054
	Brenda Holmes HFD-300	301/594-0054
GSA Cars	Administrative Staff * HFD-305	301/594-1058
Hair Growers/Hair Loss	Flora Chang HFD-312	301/594-1065
HCFA (Health Care Financing Administration) Liaison		
	Herb Gerstenzang HFD-330	301/594-0101
Homeopathy	Edward Miracco HFD-314	301/594-0070
	Jan Davis - backup HFD-314	301/594-0070
Human Subject Protection	Mary Jo Zollo HFD-343	301/594-1026
Hypophosphatemia	Robert Eshelman HFD-312	301/594-1065
Import of Drugs	Import/Export Team HFD-316	301/594-3150
Import Listing	Hea-Suk Kiel HFD-316	301/594-3150

Import Listing & Compliance Evaluations		
	Hea-Suk Kiel HFD-316	301/594-3150
Information Technology Team (OC)		
	Tom Selnekovic HFD-300	301/594-0054
	Roxana Fay HFD-310	301/594-0063
	Paul Motise HFD-320	301/594-1089
	Sid Spungen HFD-330	301/594-0101
	Matthew Tarosky HFD-340	301/594-0020
Information Technology Coordinating Committee		
	Tom Selnekovic HFD-300	301/594-0054
	Mark Lynch HFD-324	301/827-0062
EES	Mark Lynch HFD-324	301/827-0062
	John Singer HFD-324	301/827-0071
	Shirnette Ferguson HFD-324	301/827-0068
Informed Consent	Mary Jo Zollo HFD-343	301/594-1026
Ingrown Toenails	Flora Chang HFD-312	301/594-1065
Injunction Committee	Barry Rothman HFD-325	301/594-0098
Inspections (Directed)		
CGMP	John Singer HFD-324	301/827-0071
	Randall Woods HFD-324	301/827-0065
Clinical	Bette Barton, MD, PhD HFD-344	301/594-1032
IRB	Mary Jo Zollo HFD-343	301/594-1026
GLP	C.T. Viswanathan, PhD HFD-345	301/594-1023
Institutional Review Boards		
	Mary Jo Zollo HFD-343	301/594-1026
Insulin Certification	Sid Spungen HFD-333	301/594-0101
	Puri Subramaniam HFD-333	301/594-0107
International Harmonization		
	Stephanie Gray HFD-300	301/594-0054
	Bette Barton HFD-344	301/594-1032
	Pat Beers Block HFD-320	301/594-0093
	Stan W. Woollen HFD-341	301/594-0020
Internal Analgesics	Kevin Budich HFD-312	301/594-1065

Internal Deodorant Products		
	William A. Russell HFD-314	301/594-0070
Internet Drug Labeling	Roma Egli HFD-314	301/594-0070
Investigations	John Singer HFD-324	301/827-0071
	Randall Woods HFD-324	301/827-0065
In Vivo Bioequivalence	C.T. Viswanathan, PhD HFD-345	301/594-1023
IRB/Informed Consent/RDRC Issues		
IRB/Informed Consent	Mary Jo Zollo HFD-343	301/594-1026
RDRC/PET	R.K. Leedham HFD-343	301/594-1026
Technician/FOI	Nancy Pursell HFD-343	301/594-1026
IRS (Identical, Related, and Similar to DESI Drugs)		
	Herb Gerstenzang HFD-330	301/594-0101
Iron Toxicity Rule--Rx	Puri Subramaniam HFD-333	301/594-0107
	John Loh HFD-333	301/594-0101
Kits/Devices	William Nychis HFD-312	301/594-1065
Labeling Controls (CGMPs)		
	Paul Motise HFD-325	301/594-1089
Labeling (Prescription)	John Loh HFD-333	301/594-0101
	Sonia Crisp HFD-333	301/594-0101
	Puri Subramaniam HFD-333	301/594-0107
Laboratory Testing		
Non-Sterile	Russ Rutledge HFD-325	301/594-0098
	Monica Caphart HFD-325	301/594-0098
Sterile	Richard Friedman HFD-322	301/594-0095
	Michael Verdi HFD-301	301/594-0054
	Tracy Roberts HFD-325	301/594-0098
Laxatives, Antidiarrheals	Jonathan Lane HFD-312	301/594-1065
Leg Cramps (Quinine Sulfate)		
	Kevin Budich HFD-312	301/594-1065

LTE (Less Than Effective Drugs)		
	Herb Gerstenzang HFD-330	301/594-0101
Lyophilization	Richard Friedman HFD-322	301/594-0095
	Michael Verdi HFD-301	301/594-0054
Manual of Policies and Procedures Working Group		
Distribution	Anita Harrell HFD-305	301/594-1058
	Mary Thompson HFD-310	301/594-0063
	Patricia Johnson HFD-300	301/594-0054
	Carolyn Hommel HFD-340	301/594-0020
Manufacturing Pharmacy (see Pharmacy Compounding)		
Medical Gases	Duane Sylvia HFD-325	301/594-0095
	Michael Verdi HFD-301	301/594-0054
Medical Imaging	R.K. Leedham HFD-343	301/594-1026
MERS (Medication Error Sub-Committee)		
	Puri Subramaniam HFD-333	301/594-0107
	LuAnn Pallas HFD-325	301/594-0098
Menstrual Drug Products (Diuretics)		
	William Nychis HFD-312	301/594-1065
Mercury Containing Topical Antimicrobials		
	Kevin Budich HFD-312	301/594-1065
Methadone/LAAM	Elsworth Dory HFD-342	301/594-1029
Nail Biting/Thumbsucking	Constance E. Bulawka HFD-312	301/594-1065
Narcotic Treatment Program		
	Elsworth Dory HFD-342	301/594-1029
Narcotic Treatment Program Policy Review Board (Interagency)		
	Betty Jones HFD-301	301/594-0054
	Elsworth Dory HFD-342	30/1594-1029

NDA/ANDA Pre-Approval Inspections		
	Bruce Hartman HFD-324	301/827-0067
	Mark Lynch HFD-324	301/827-0062
	Randall Woods HFD-324	301/594-0065
	John Singer HFD-324	301/827-0071
New Drug Issues		
OTC	Robert Eshelman HFD-312	301/594-1065
Prescription	John Loh HFD-333	301/594-0101
	Ray Fazzari HFD-330	301/594-0101
	Ada Irizarry HFD-330	301/594-0101
	Mel Szymanski HFD-332	301/594-2073
Nonclinical Laboratory Studies		
	C. T. Viswanathan, PhD HFD-345	301/594-1023
Nontraditional Drug (NTD) Labeling		
	NTD Compliance Team HFD-314	301/594-0070
OAI (Official Action Indicated) Liaison		
	Shirnette Ferguson HFD-324	301/827-0068
	Janine D'Ambrogio HFD-324	301/827-0069
OCI (Office of Criminal Investigations) Liaison		
	Bradford W. Williams HFD-310	301/594-0063
	Nick Buhay HFD-325	301/594-0098
Offshore Pharmacy	Don Leggett HFD-316	301/594-3150
Ophthalmics	Jonathan Lane HFD-312	301/594-1065
ORA Workplan	Betty Jones HFD-301	301/594-0054
Oral Discomfort	Robert Eshelman HFD-312	301/594-1065
Oral Mucosal	Robert Eshelman HFD-312	301/594-1065
OTC Drug Labeling	Robert Eshelman HFD-312	301/594-1065
Overindulgence with Alcohol/Food		
	William Nychis HFD-312	301/594-1065

PAG (Program Administrative Group)		
	Betty Jones HFD-301	301/594-0054
Parking Spaces	Administrative Staff * HFD-305	301/594-1058
Payroll	Administrative Staff * HFD-305	301/594-1058
PDMA (Prescription Drug Marketing Act)		
	Margaret O'Rourke HFD-330	301/594-0101
Loss and Theft Reports		
	Betty McRoy HFD-330	301/594-0101
Pediculicides	Robert Eshelman HFD-312	301/594-1065
Peer Review Committee Representatives		
CSO	Bradford W. Williams HFD-310	301/594-0063
Medical Officer	Frances O. Kelsey, MD HFD-300	301/594-0054
Scientific	C.T. Viswanathan, PhD HFD-345	301/594-1023
Penicillin Cross Contamination		
	Duane Sylvia HFD-325	301/594-0098
	Edwin Melendez HFD-325	301/594-0098
Personal Importation Issues		
	Jim Hamilton HFD-316	301/594-3150
PET Radiopharmaceuticals (Positron Emission Tomography)		
CGMPs	R.K. Leedham HFD-343	301/594-1026
	Michael Verdi HFD-301	301/594-0054
RDRC Review	R.K. Leedham HFD-343	301/594-1026
New Drug Issues	Mel Szymanski HFD-332	301/594-0101
	Ray Fazzari HFD-330	301/594-0101
Pharmacy Compounding	Kathleen Anderson HFD-332	301/594-0101
	Robert Tonelli HFD-332	301/594-0101
	Rita Hoffman HFD-332	301/594-0101
	Fred Richman HFD-332	301/594-2073
Pharmacokinetics	C.T. Viswanathan, PhD HFD-345	301/594-1023
Policy and Advisory Opinions on Import/Export		
	Jim Hamilton HFD-316	301/594-3150

Pre-Approval Program	Mark Lynch HFD-324	301/827-0072
	Melissa Egas HFD-324	301/594-0095
Guidance	Pat Beers Block HFD-320	301/594-0093
Pregnancy Warning	Jonathan Lane HFD-312	301/594-1065
Prescription Drug Labeling		
	John Loh HFD-333	301/594-0101
	Puri Subrmaniam HFD-333	301/594-0107
	Sonia Crisp HFD-333	301/594-0101
Process Validation		
General	Paul Motise HFD-325	301/594-1089
Non-Sterile Dosage Forms		
	John Dietrick HFD-324	301/594-0095
Sterile Dosage Forms	Richard Friedman HFD-322	301/594-0095
	Michael Verdi HFD-301	301/594-0054
	Tracy Roberts HFD-325	301/594-0098
Project Management Coordinating Committees/Subcommittees		
	Betty Jones HFD-301	301/594-0054
	Jackie Leung HFD-310	301/594-0063
	Pat Beers Block HFD-320	301/594-0093
	Lana J. Ragazinsky HFD-336	301/594-0107
	Marilyn Wolf HFD-316	301/594-3150
Project Managers	Brenda Holmes HFD 300	301/594-0054
	Jackie Leung HFD-310	301/594-0063
	Marilyn Wolf HFD-316	301/594-3150
	Pat Beers Block HFD-320	301/594-0093
	Lana J. Ragazinsky HFD-336	301/594-0107
	Carolyn Hommel HFD-341	301/594-0020
	Mathew Tarosky HFD-340	301/594-0020
RDRCs (Radioactive Drug Research Committee)		
	R.K. Leedham HFD-343	301/594-1026
Recalls	Michael Verdi HFD-301	301/594-0054
Recycling Plastic Drug Product Containers		
	Paul Motise HFD-325	301/594-0098

Registration & Listing Policy		
OTC Products	Jackie Leung HFD-310	301/594-0063
Prescription Products	Herb Gerstenzang HFD-330	301/594-0101
Repackaging	Barry Rothman HFD-325	301/594-0098
	Edwin Melendez HFD-325	301/594-0095
Salvaging	Paul Motise HFD-325	301/594-0098
Security and Exchange Commission Filing		
	Betty Jones HFD-301	301/594-0054
Skin Bleaching	Flora Chang HFD-312	301/594-1065
Skin Protectants/Lotion	Kevin Budich HFD-312	301/594-1065
Sleep Aids/Sedatives	William Nychis HFD-312	301/594-1065
Sobriety Aids (Inebriation)	William A. Russell HFD-314	301/594-0070
Software Policy Task Force (FDA)		
	Paul Motise HFD-325	301/594-0098
Special Investigations	John Singer HFD-324	301/827-0071
	Randall Woods HFD-324	301/827-0065
	Mel Szymanski HFD-332	301/594-0101
	Margaret O'Rourke HFD-330	301/594-0101
	Ada Irizarry HFD-330	301/594-0101
Sponsors & Monitors	Carolanne Currier HFD-344	301/594-1032
Stability and Expiration Dating		
	Barry Rothman HFD-325	301/594-0095
Sterile Facility Construction (Clean Rooms)		
	Richard Friedman HFD-322	301/594-0095
	Michael Verdi HFD-301	301/594-0054
	Tracy Roberts HFD-325	301/594-0098
Sterilization Validation	Richard Friedman HFD-322	301/594-0095
	Michael Verdi HFD-301	301/594-0054
	Tracy Roberts HFD-325	301/594-0098

Stimulants	William Nychis HFD-312	301/594-1065
Sunscreens	Constance E. Bulawka HFD-312	301/594-1065
Sweet Spirit of Nitre	Edward Miracco HFD-314	301/594-0070
TRP (Tamper-Resistant Packaging)		
Labeling	Robert Eshelman HFD-312	301/594-1065
Packaging	Lana J. Ragazinsky HFD-336	301/594-0107
TIACC (Therapeutic Inequivalence Action Coordination Committee)		
	Roger Gregorio HFD-336	301/594-0107
Tobacco Products & Smoking Deterrents		
	Kevin Budich HFD-312	301/594-1065
Toothpaste	Robert Eshelman HFD-312	301/594-1065
Topical Antibiotics/Analgesics		
	Jonathan Lane HFD-312	301/594-1065
Topical Antifungal Products		
	Flora Chang HFD-312	301/594-1065
Topical Antimicrobials	Kevin Budich HFD-312	301/594-1065
Topical Drugs	Randall Woods HFD-324	301/827-0065
Topical Hormone Products		
	Roma Egli HFD-314	301/594-0070
Topical Otic Products	Jonathan Lane HFD-312	301/594-1065
Training	Administrative Staff * HFD-305	301/594-1058
Transdermals	Brian Hasselbalch HFD-325	301/594-0098
Travel	Administrative Staff * HFD-305	301/594-1058

Unapproved New Drugs		
OTC	Bradford W. Williams HFD-310	301/594-0063
Pre-1962 Rx Products	Herb Gerstenzang HFD-330	301/594-0101
Prescription	Ray Fazzari HFD-330	301/594-0101
	Ada Irizarry HFD-330	301/594-0101
	Mel Szymanski HFD-300	301/594-2073
Vaginal Contraceptives	William Nychis HFD-312	301/594-1065
Vaginal Products	William Nychis HFD-312	301/594-1065
Validation	John Dietrick HFD-322	301/594-0095
Videoconferencing	Russ Rutledge HFD-325	301/594-0098
	Paul Motise HFD-325	301/594-0098
Vitamin/Mineral & Hematinics		
	William Nychis HFD-312	301/594-1065
Wart Remover	Constance E. Bulawka HFD-312	301/594-1065
Water Quality	Richard Friedman HFD-322	301/594-0095
	Pat Alcock HFD-322	301/594-0095
	Michael Verdi HFD-301	301/594-0054
	Tracy Roberts HFD-325	301/594-0098
Weight Control Products	Jan Davis HFD-314	301/594-0070
World Wide Web Work Group (FDA)		
	Paul Motise HFD-325	301/594-1089
	Randall Woods HFD-324	301/827-0065
	Pat Beers Block HFD-320	301/594-0093

***** HFD-300, 310, 340--Program Support-- Peggy Noland
HFD-320, 330--Program Support--Linda McGee